The American Journal of Medicine

September 1953

The American Journal of Medicine

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Change of address must reach us one month preceding month of issue.

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The American Journal of Medicine

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Editorial

Clinical Studies

In this ingeniously planned investigation Dr. Bing and his colleagues attempt to utilize the technic of catheterization of the coronary sinus for *in vivo* study of the metabolic requirements of the heart in normal human subjects and in low output and high output failure. The present paper presents the results in regard to the over-all aerobic metabolism of glucose, lactate and pyruvate as measured by oxygen extraction ratios and the estimated conversion of oxidative energy from these carbohydrates into cardiac work. A number of assumptions are necessary, of course, but the inferences drawn are of considerable interest. Among these is the conclusion that in heart failure glucose and lactate are metabolized adequately but the energy derived from their oxidation is not as efficiently utilized for cardiac work.

This unusually interesting paper brings out several important points in relation both to the mechanisms of relief of cyanosis and dyspnea in patients with tetralogy of Fallot by squatting and certain other postures, and in regard to practical utilization in diagnosis and management. Beneficial postural effects are shown to derive from an increase in the volume of venous return with consequent improvement in oxygen saturation of the mixed venous blood. Instead of relying simply on a history of squatting, the author proposes that the beneficial effects of favorable postures be demonstrated as part of the regular preoperative evaluation of the patient: those who show a good response in the typical postures will do well following systemic-pulmonary anastomosis. Before operation the benefits of posturing can thus be utilized maximally by intelligent exploitation of the principles involved.

Using venographic technics, the authors studied the effects of the Valsalva maneuver on arrest and reversal of venous blood flow. The observations throw light upon the axillary and subclavian veins as sites of predilection for vein thrombosis following effort. Of special interest is the additional confirmation afforded concerning the important role of the valveless vertebral vein system in the spread of metastases.

Contents continued on page 5

in headache

prompt...prolonged...prescribed pain relief

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Every patient with essential hypertension is a potential candidate for Raudixin therapy

Because of its safety and the stability of its hypotensive effect, Raudixin can be confidently prescribed for all patients with essential hypertension. It is especially recommended for the large, indeterminate group whose symptoms are not severe enough to warrant the use of other hypotensive agents. Critical adjustment of dosage is unnecessary.

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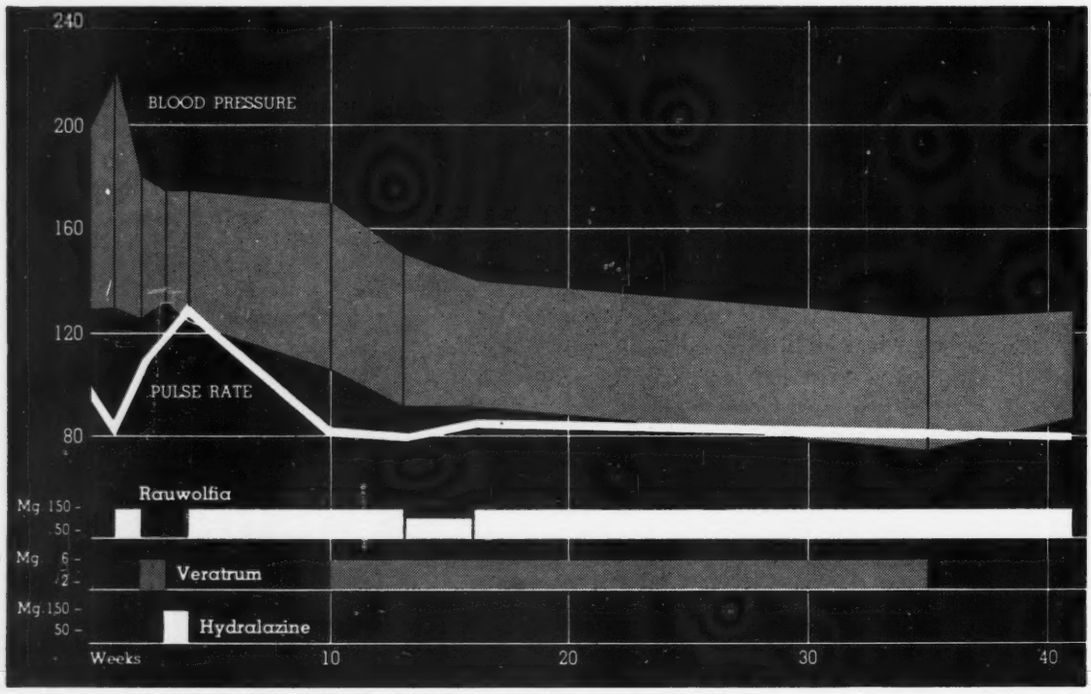

This patient's blood pressure was lowered about the same amount by rauwolfia, veratrum or hydralazine. Hydralazine, however, caused undesirable reactions and increased the pulse rate. Veratrum augmented the effect of rauwolfia, and the effect was maintained even when veratrum was discontinued some months later. – After R. W. Wilkins, Ann. Int. Med. 37: 1144, 1952.

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50 mg. tablets, bottles of 100 and 1000

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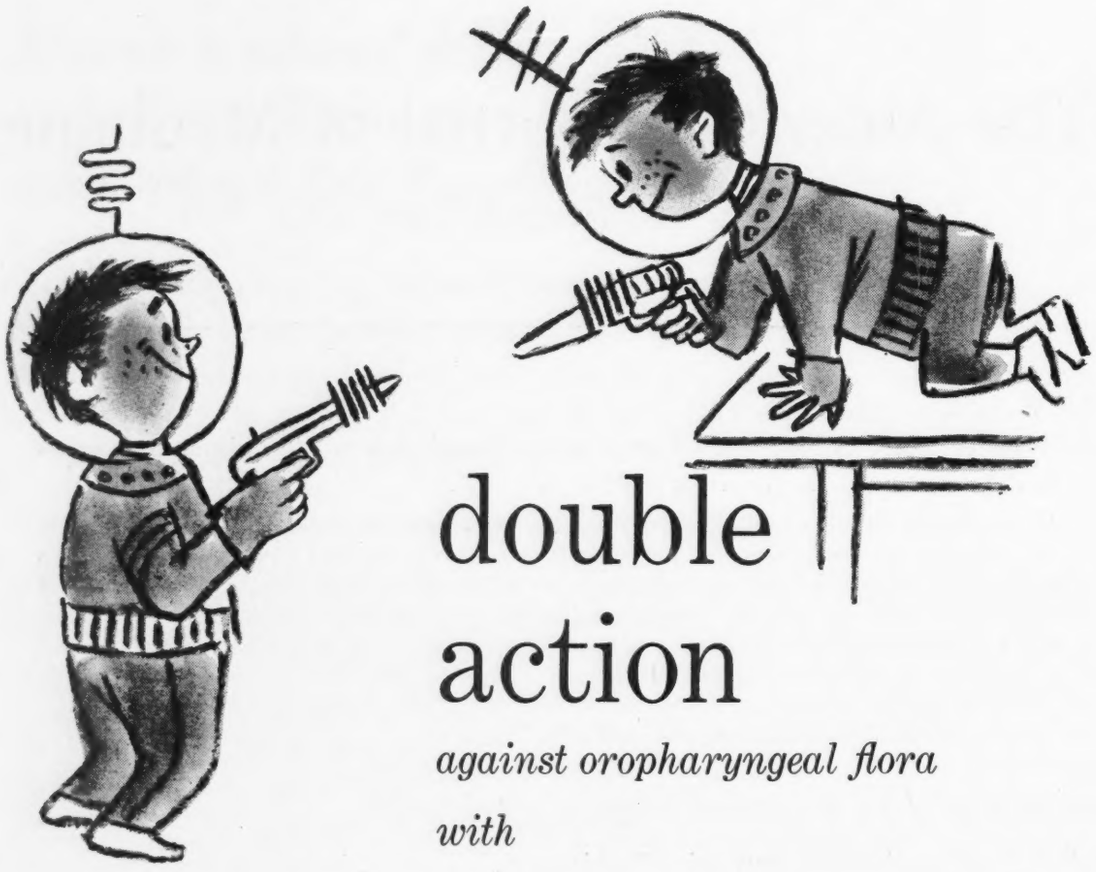

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Correction: In the Symposium on Drug Addiction which appeared in the May, 1953 issue of The American Journal of Medicine, the registered trade-mark symbol (R) was applied incorrectly to the following non-proprietary drug designations: methadone, pethidine, metopon, 6-methyldihydromorphine, meperidine, cannabinol, peyote, paraldehyde, N-methylmorphinan and phenobarbital.

Advertising Index on 3rd Cover

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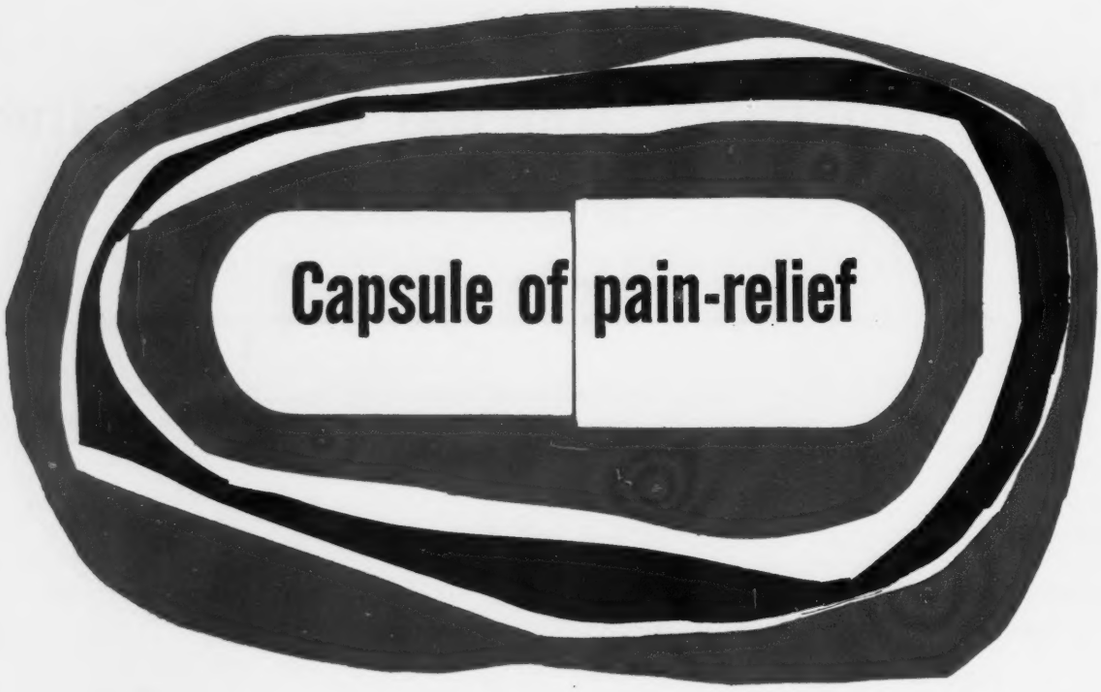

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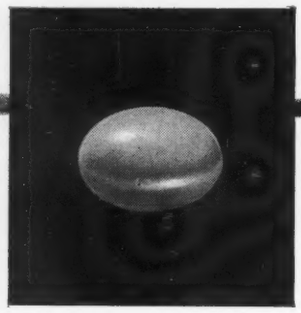

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Sulfadiazine.....0.083 Gm.
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1. Davis, B. D. : Pub. Health Rep. 67 : 376-379 (April) 1952.

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indicated in

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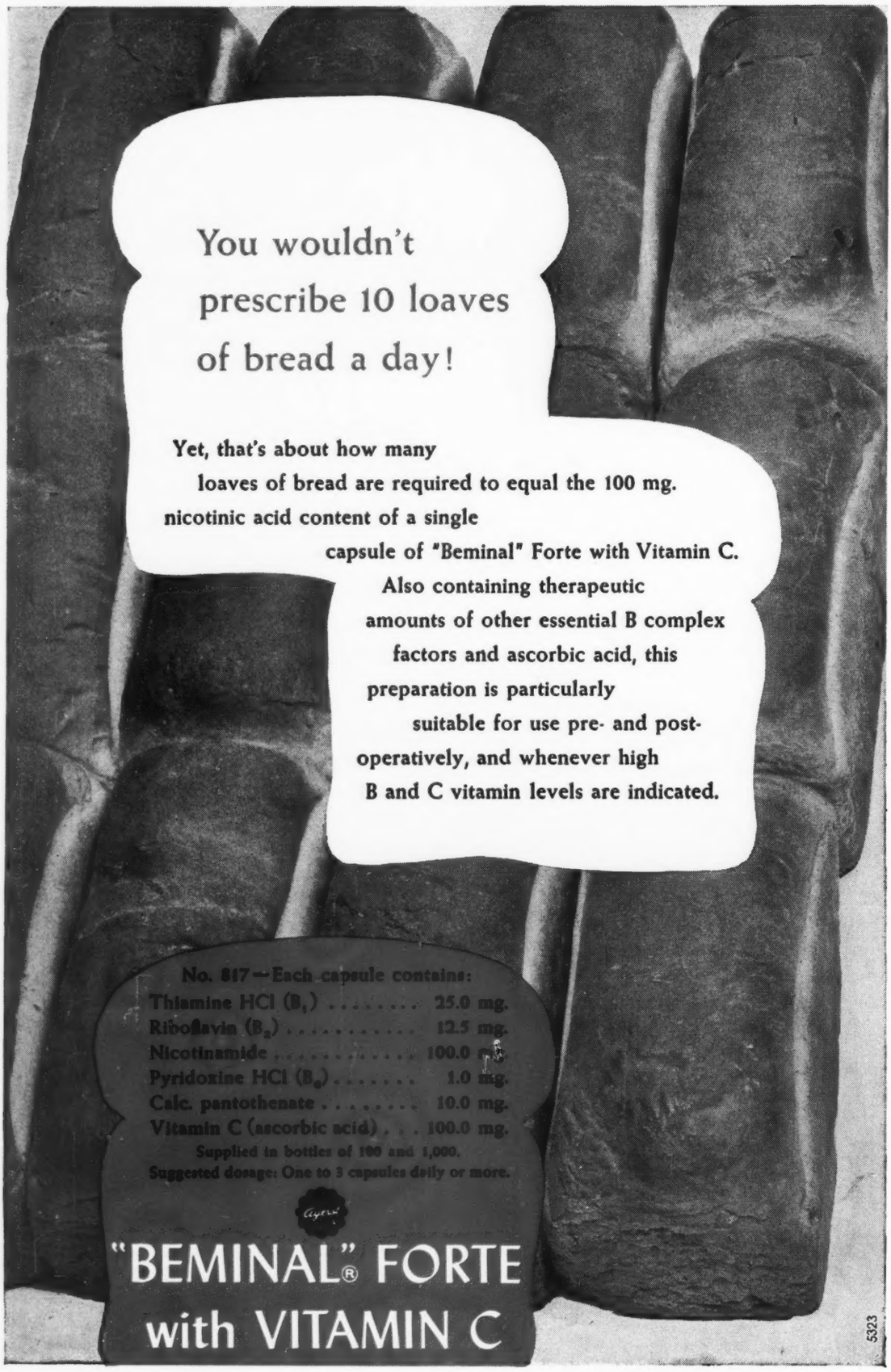
Gram-positive infections, especially those due to staphylococci, streptococci, and pneumococci (e.g., pneumonia, pharyngitis, tonsillitis, scarlet fever, erysipelas, osteomyelitis, pyoderma).

mixed infections, including those of the urinary and respiratory tracts.



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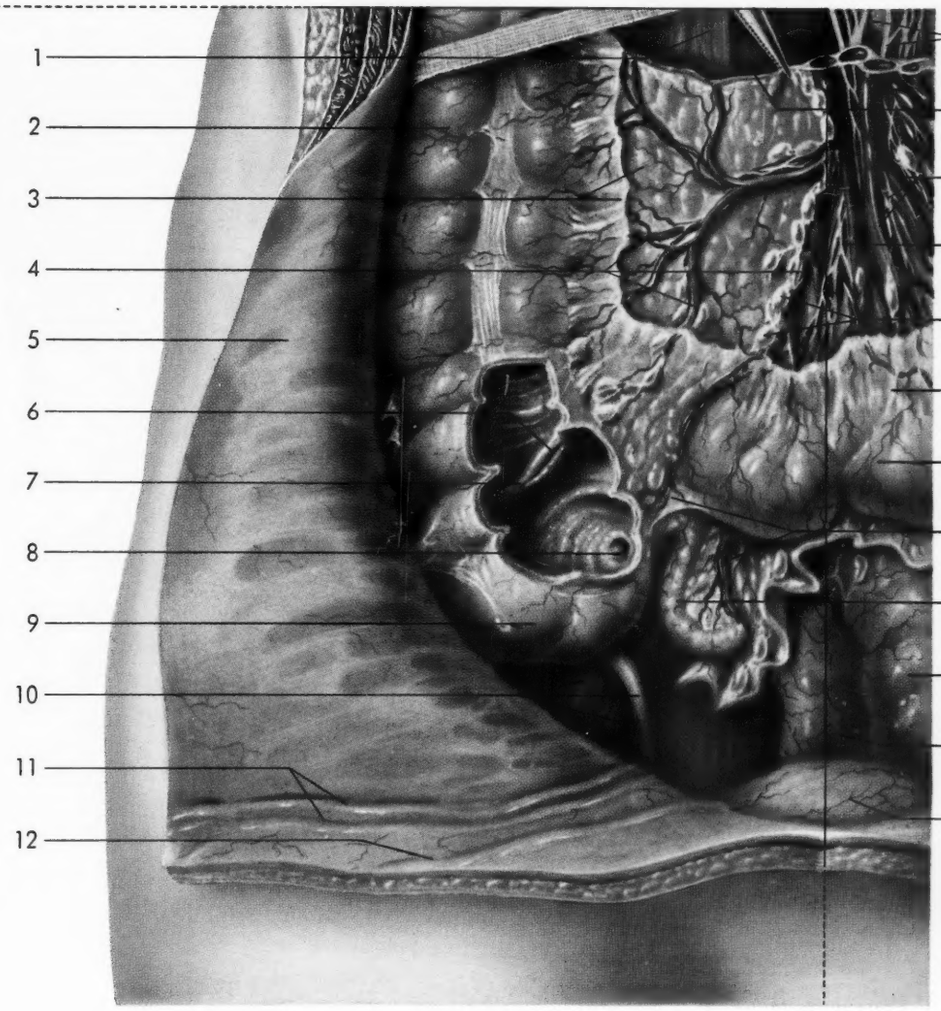
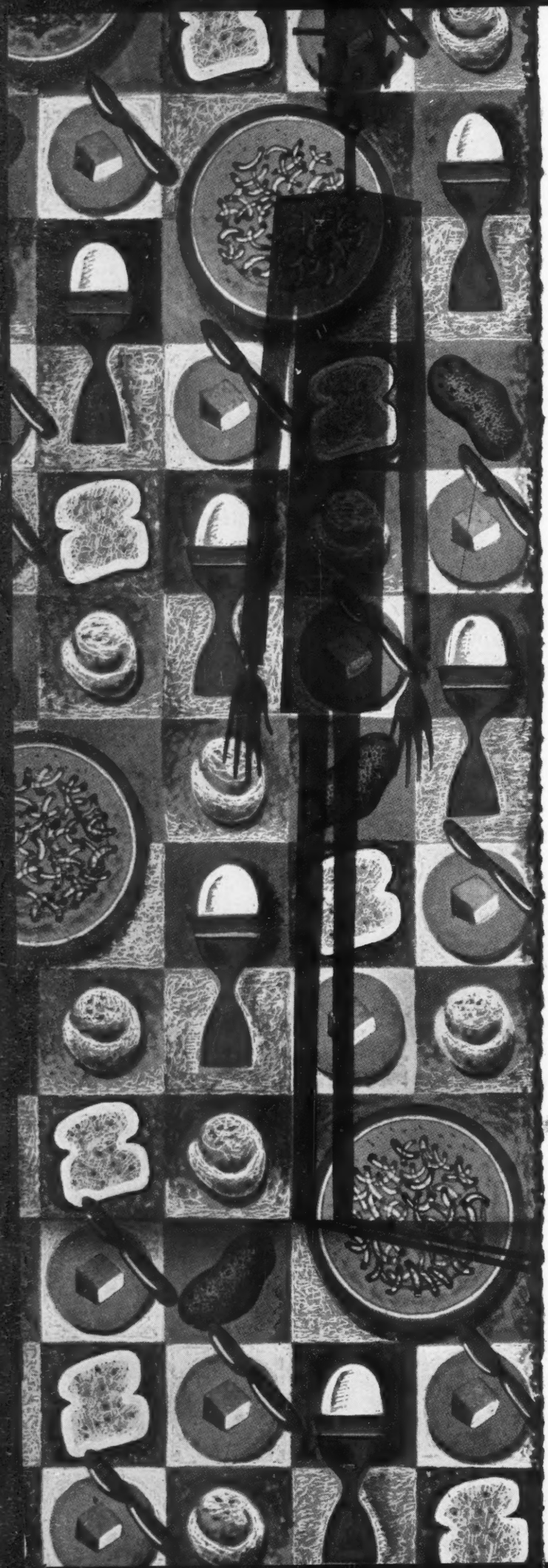
Lower Right Quadrant of the Abdomen



1 Spermatic artery and vein
2 Ascending colon
3 Mesocolon
4 Branches of ileocolic artery and vein
5 Parietal peritoneum
6 Ileocecal valve
7 Frenum
8 Appendicocecal valve
9 Cecum
10 Ureter and external iliac artery and vein
11 Epigastric artery and vein
12 Lateral umbilical ligament
13 Aorta and abdominal aortic plexus
14 Vena cava
15 Intestinal arteries and veins
16 Sympathetic abdominal plexus
17 Ileocecal lymph nodes
18 Mesentery
19 Ileum
20 Ileocecal fold and appendicular artery and vein
21 Vermiform appendix
22 Sigmoid colon
23 Rectum
24 Urinary bladder

This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Lederle



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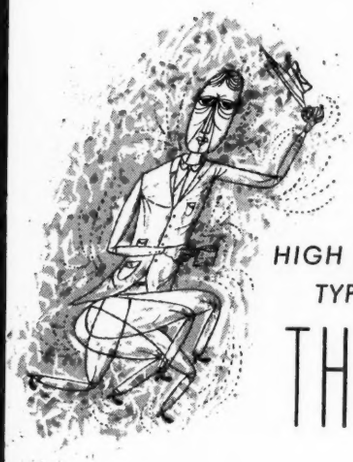

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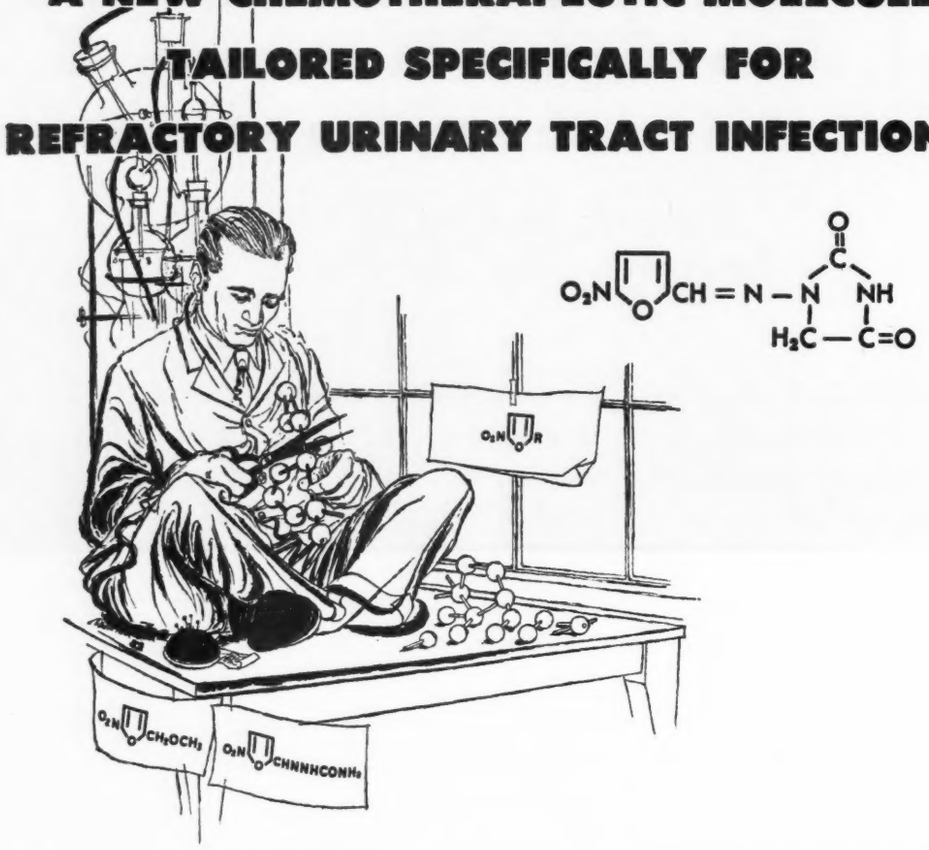
A NEW CHEMOTHERAPEUTIC MOLECULE TAILORED SPECIFICALLY FOR REFRACTORY URINARY TRACT INFECTIONS



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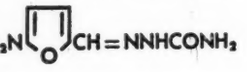
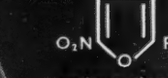


Now we have succeeded in chemically tailoring a unique molecule, designed specifically for the treatment of bacterial urinary tract infections:

The NITROFURANS



A unique class of antimicrobials

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N-(5-nitro-2-furfurylidene)-1-aminohydantoin.

for { **pyelonephritis**
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pyelitis

which have proven refractory to other antibacterial agents:

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provides definite advantages:

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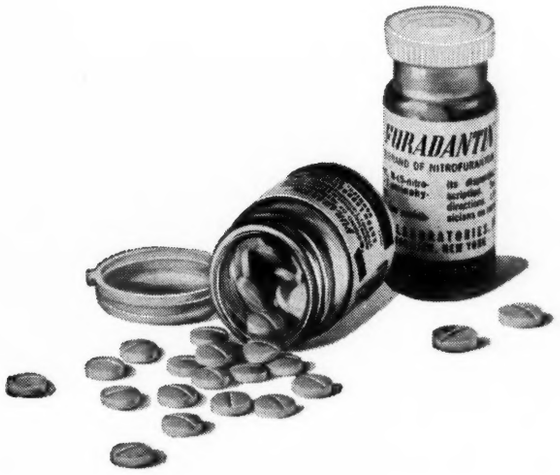
- *tailored specifically for urologic use*



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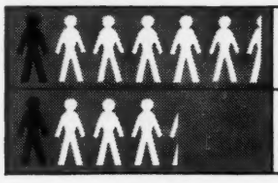

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†Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953. *Trademark

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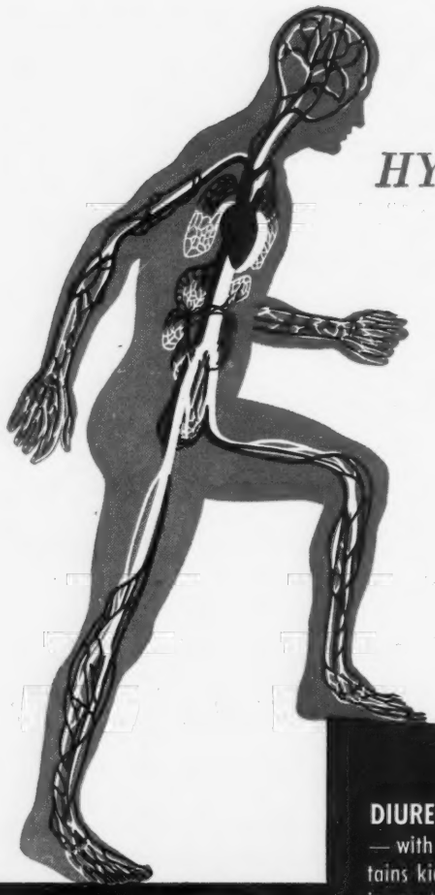

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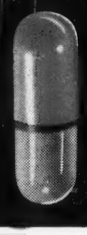

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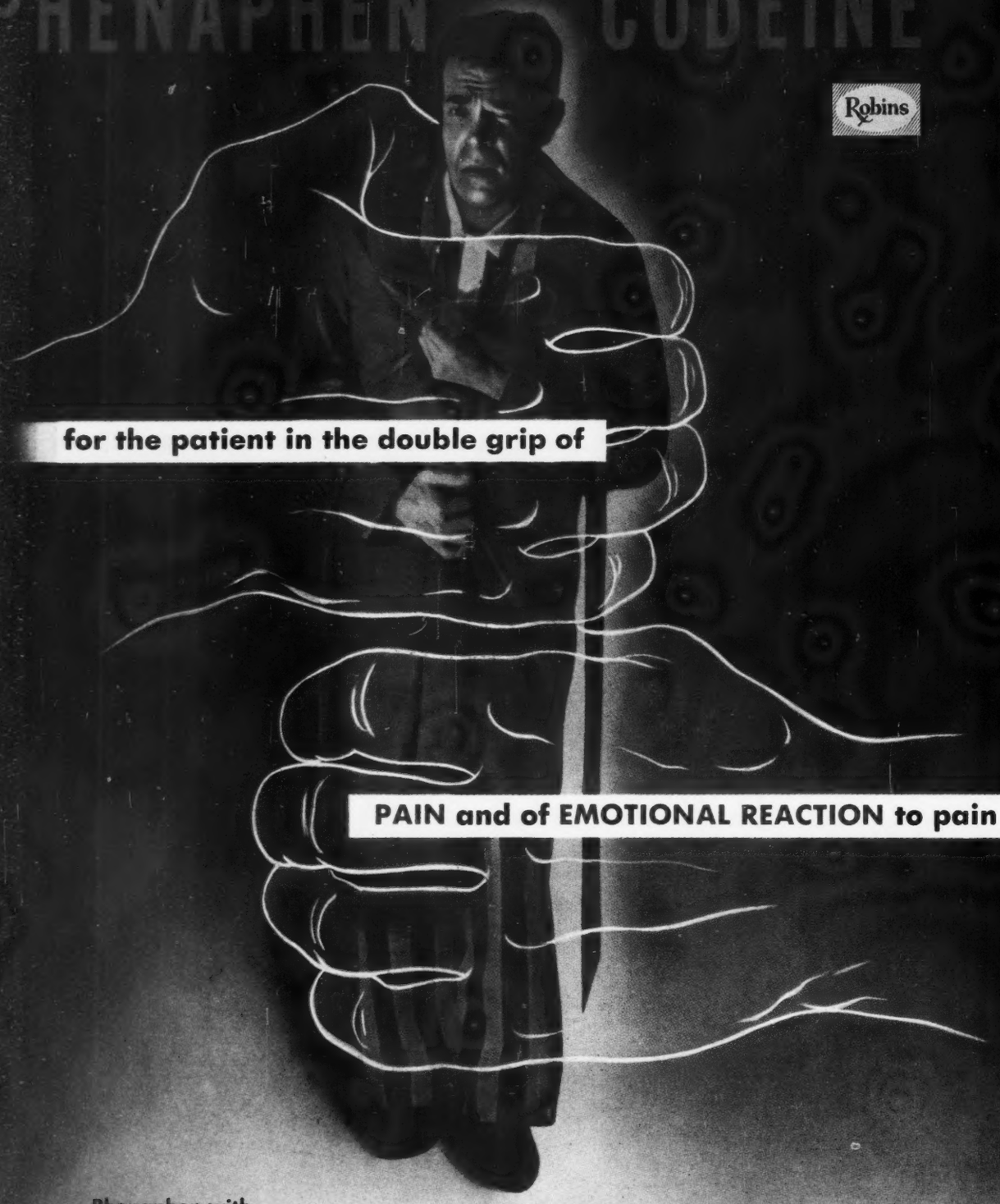

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PAIN and of EMOTIONAL REACTION to pain

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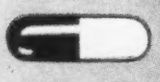

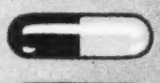

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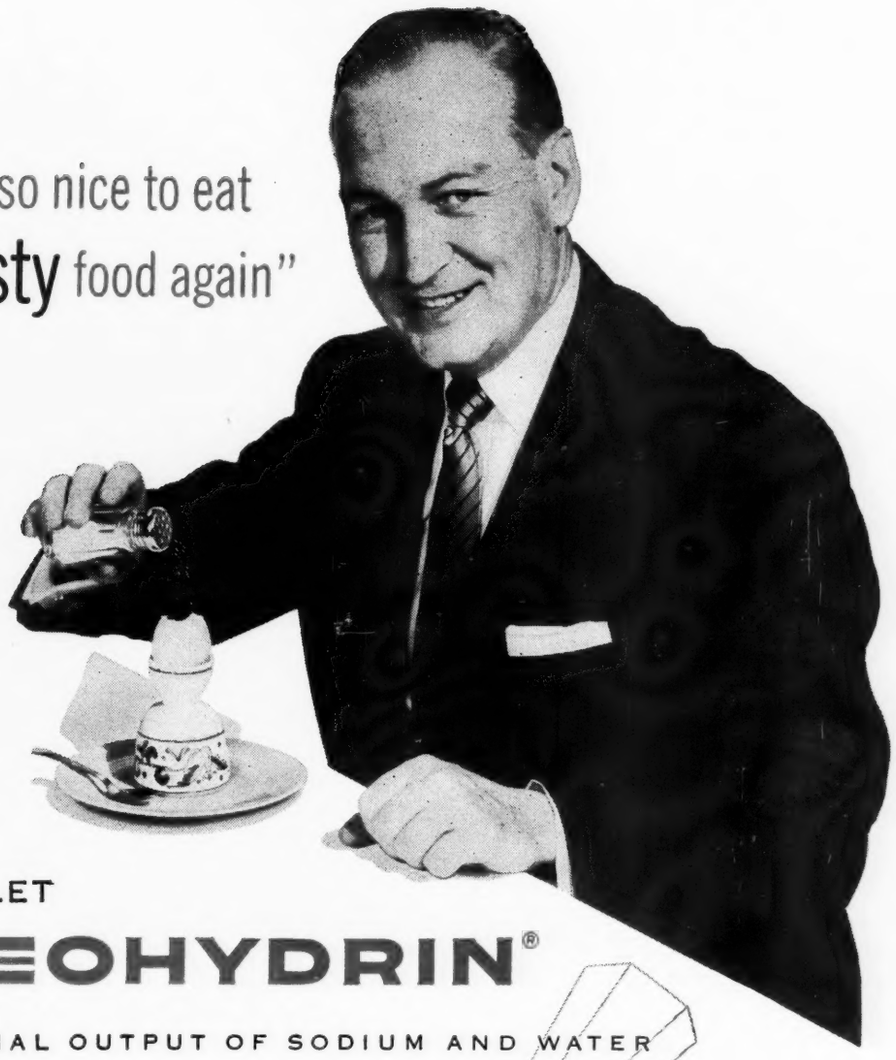
Phenaphen with Codeine Phosphate ½ Gr.
(Phenaphen No. 3)



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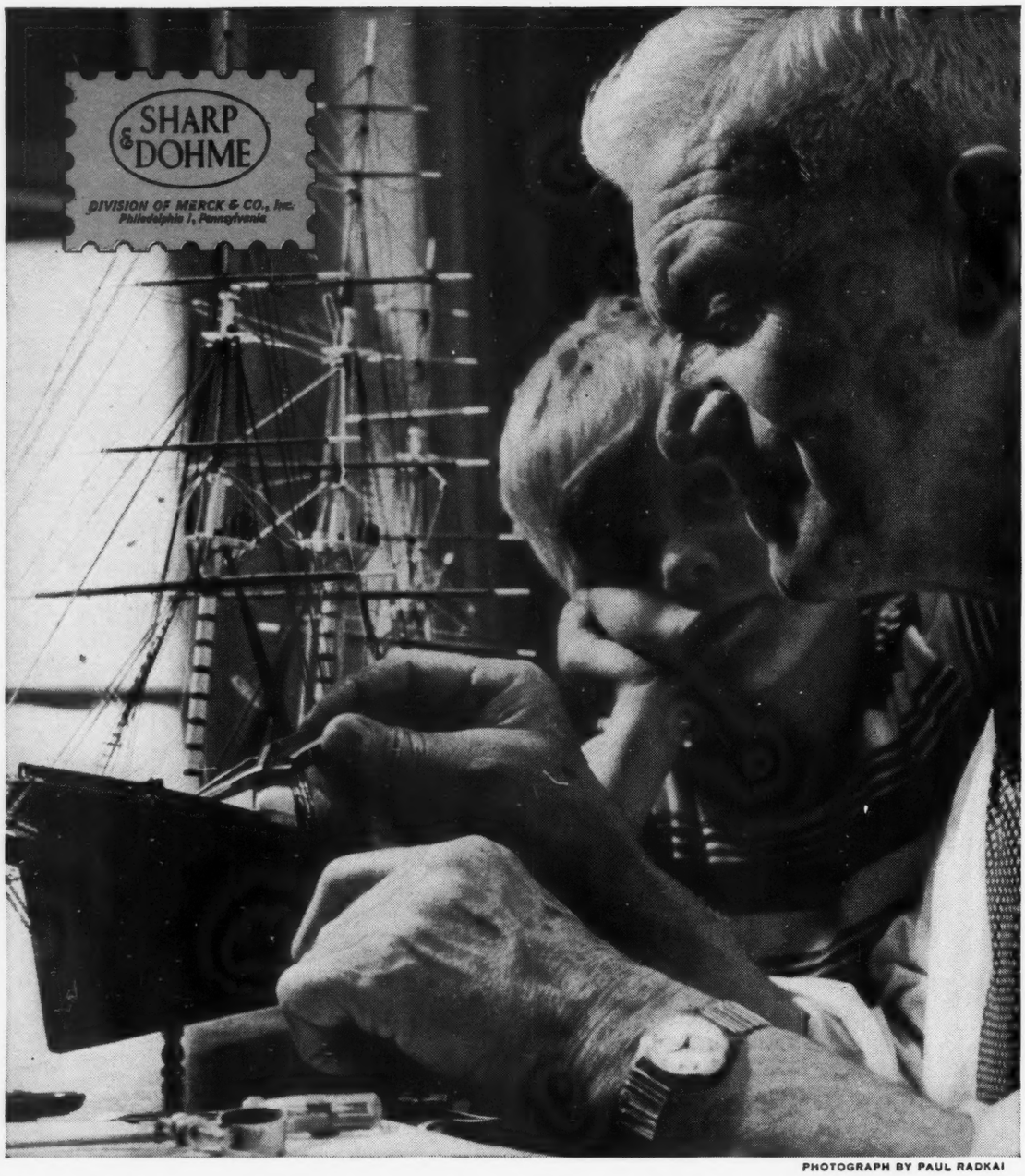

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SYNGESTERONE* IN SESAME OIL	Progesterone, U.S.P., in Sesame Oil 10 mg., 25 mg., 50 mg. and 100 mg. per cc.; in single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
SYNGESTERONE* IN AQUEOUS SUSPENSION	Progesterone, U.S.P.. in Aqueous Suspension 25 mg. and 50 mg. per cc.; in 10 cc. multiple-dose vials
COMBANDRIN*	Estradiol Benzoate, U.S.P., 1 mg. and Testosterone Propionate, U.S.P., in Sesame Oil 20 mg. per cc. In single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
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Editorial

Heart Failure

In his recent Oliver Sharpey lectures on the Dynamics of Heart Failure, John McMichael reviews the facts which enter into his concept of two types of congestive failure, one characterized by low cardiac output and one by a high output. In each type the venous pressure, in determining the degree of diastolic stretching of the cardiac muscle fiber, also determines the energy released in systole in accordance with Starling's law. If the muscle fiber is overstretched in diastole, the energy of systole is submaximal, thus elevated venous filling pressure may result in a lessened cardiac output. In such circumstances reduction of venous pressure generally increases the output. In "high output failure" a relatively strong myocardium is overwhelmed by a high venous pressure; in low output failures a weakened muscle may be overstretched by much lower venous pressures. The "high output" failures are due to extracardiac causes, the "low" to intrinsic cardiac lesions.

In 1951 McCann reviewed the role of the lung in interposing a variable resistance to blood flow between the right and left ventricles, pointing out that such a resistance makes it necessary to apply Starling's law to each ventricle separately. This pulmonary resistance may rise to such a degree during paroxysms of coughing that syncope results from the decreased output of the left ventricle, "tussive syncope" (1949).

There can be little doubt that a similar syncope develops in anaphylactic shock, severe asthma, during pressure breathing and any sharp elevation of intra-alveolar pressure. The discovery by von Euler and Liljestrand that anoxia caused a rise in the pulmonary arterial pressure in the cat led to the work of Dirken and Heemstra, who showed that pulmonary vascular resistance was increased by the formation of histamine in the lungs of animals, and that this could be counteracted by antihistamines. Durwood Smith showed that histamine produces great constrictor effects on isolated pulmonary vessels and veins. The effect of histamine upon the bronchi in precipitating asthma is well known. Thus it is possible that severe anoxia, through histamine, may elevate the resistance of the lung to a point at which the output of the left ventricle decreases while the venous pressure rises, and congestive failure of the circulation takes place. It is significant in this connection that Levy and Berne, in Carl Wigger's laboratory, were able to produce congestive failure experimentally by one means only, that of mechanically constricting the pulmonary artery by a band. Many types of injury of the left ventricular muscle resulted only in shock; an increase in pulmonary resistance led to congestive failure.

Every clinical observer is aware that the initial phases of myocardial infarction are characterized by the phenomena of shock rather than those of congestive failure. If congestion occurs later, may it not then depend upon adaptive reactions taking place within the lungs?

Let us suppose that a weakened left ventricle is faced with a stress in which it is unable to put out enough blood to support the oxygen demand of the cells of the body, so that an oxygen deficiency occurs. The first reaction to oxygen lack (Dill), as when an unacclimatized man ascends a high mountain, is that of a hyperventilation which lowers the arterial pCO_2 and slightly elevates the arterial pH until such time as other adaptive reactions set in. The initial anoxic hyperventilation is probably brought about by stimuli sent in to the respiratory center from widely distributed chemoreceptors, described in recent reviews by Heymans and by Pi-Suñer.

Yandell Henderson (1943) pointed out long ago that anoxia in some instances leads to hypocapnia and shock, as in carbon monoxide poisoning and lobar pneumonia, while in other

instances, such as in bronchopneumonias, the circulation may fail with venous congestion. He was inclined to attribute this difference to the CO_2 tension and its relationship to the venopressor mechanism. In 1917, in a study of cardiac dyspnea, J. P. Peters sought the explanation of the low CO_2 tension of the alveolar air. Peters and Barr found the arterial pCO_2 of patients with congestive heart failure to be from 39.7 to 52.2 mm. Hg, and noted a consistently high gradient between arterial blood and alveolar air. Examination of the data of Meakins, Dautreband and Fetter reveals that in the case of breathless patients with mitral stenosis, who were not in congestive failure, the pCO_2 was less than normal and rose as signs of congestive failure developed. In his study of cardiac asthma Harrison records low values of arterial pCO_2 associated with hyperventilation. If the ventilation were diminished by administration of morphine, the arterial pCO_2 rose.

These earlier studies were conducted under considerable difficulty. The pCO_2 had to be determined by locating the arterial CO_2 content on a CO_2 dissociation curve of the patient's blood, and the pH of blood was calculated from Hasselbach's equation. In spite of these difficulties one finds much to support the hypothesis that the initial anoxia of primary or left-sided heart failure led to hyperventilation and hypocapnia, and that congestive failure did not appear until an adaptive reaction in the lungs had brought about a retention of CO_2 so as to bring the arterial tension of this gas to normal or higher levels.

This offers an explanation of the suddenly occurring nocturnal paroxysms of asthma which so frequently precede frank congestive heart failure. This hypothesis is supported by the facts that if the ventilation is depressed by morphine the attack of cardiac asthma may be relieved. It is further supported by the observations which Hurtado, Kaltreider and McCann made on themselves in a low pressure chamber, where it was found that a rise in residual air and a decrease in vital capacity occurred in response to reduction of the atmospheric pressure to one-half. This may now be interpreted as a mechanism for conserving carbon dioxide when hyperventilation threatens homeostasis.

It is the purpose of the writer to point out the consequences of the tendency of most recent students of heart failure to omit carbon dioxide from their calculations. This is well exemplified in the study of heart failure by J. M. Little who centered his attention on the inadequate delivery to the cells of the body of enough oxygen to satisfy the demands of their metabolism. Also Cournand in his Hamburger Lecture on the pulmonary circulation gives major attention to the factor of oxygen lack with little or no discussion of the CO_2 factor. More recently Westcott and co-workers in a study of the relation of anoxia and pulmonary resistance paid little attention to the CO_2 tension, except that they observed the effect of giving 5 per cent CO_2 in the inspired air to normal subjects. They found, as we have, that in normal subjects the effects of inspired CO_2 are variable and slight. Recent studies by Yu, Lovejoy, Joos, Nye and McCann made on eighteen patients with emphysema showed the highest correlation between arterial pCO_2 and pulmonary resistance, a positive coefficient of 0.742 being obtained, as compared with -0.085 in the case of the arterial pO_2 and of -0.318 in the case of arterial oxygen saturation. Other determinants highly correlated with pulmonary resistance were mixed venous pCO_2, residual volume and the cardiac index. When CO_2 was added to the inspired air of patients already anoxic the effects on pulmonary resistance were greatly enhanced.

Carbon dioxide is a powerful pharmacodynamic agent. Its circulatory effects are such that hypocapnia tends to slow the rate and volume of blood flow, while hypercapnia tends to accelerate them. High CO_2 tensions exert narcotic effects on the respiratory center, which may so overbalance the tendency of anoxia to increase ventilation as to bring about ventilatory failure with CO_2 acidosis and marked increase in intracranial pressure.

If students of heart failure will employ the readily available means of determining directly the tensions of *both* respiratory gases, we may soon have the answer to the riddle of Yandell Henderson's observations, particularly if attention is directed toward the inception of left ventricular failure before the phenomena of congestion are manifest. One may venture to advance the hypothesis that heart failure is first manifest by anoxic hyperventilation, hypocapnia and shock, to which the bronchi and vessels of the lung react in such a manner as to increase the pulmonary resistance to transfer of blood from right ventricle to left, with the result that filling pressure of the right side rises as the out-

put of the left ventricle is reduced. Whether right or wrong, the testing of this hypothesis should clarify many of the problems of heart failure.

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WILLIAM S. MCCANN, M.D.

Clinical Studies

Metabolic Studies on the Human Heart in Vivo*

I. Studies on Carbohydrate Metabolism of the Human Heart

R. J. Bing, M.D., A. Siegel, B.A., A. Vitale, M.D., F. Balboni, M.D., E. Sparks, M.D., M. Taeschler, M.D., M. Klapper, M.D. *and* S. Edwards, M.D.

Birmingham, Alabama

Studies on the carbohydrate metabolism have, in the past, mainly been carried out on the dog's heart *in vitro*, using either the heart-lung preparation or the heart oxygenator system. Using these procedures it has been found by Cruickshank that the dog's heart uses approximately 455 mg. of glucose/100 gm./hour.[1] Smaller values of 200 mg./100 gm./hour were obtained by Patterson and Starling.[2] Evans et al., using the heart oxygenator system, found a glucose consumption of 70 mg./100 gm./hour.[3] These investigators were of the opinion that the higher figures obtained in the heart-lung preparation resulted from the fact that the lung destroys far more glucose than one might expect from the low oxygen usage of this organ. Extraction of lactate by the heart muscle has been demonstrated by Himwich and coworkers[4] and by Evans.[5] The latter believed that the myocardial glucose and lactate extractions are a function of the arterial glucose concentration. This contrasts with the views of McGinty who found myocardial lactate extraction to be independent of the arterial lactate concentration.[6] Bogue et al. found that the isolated dog's heart removed from the circulating blood more lactic acid than any other substance[7] and that lactate is utilized for direct combustion while sugar is primarily utilized for the formation of glycogen. Myocardial usage of pyruvate was first shown by Braun-Menendez.[8]

The relative importance of carbohydrates as a source for cardiac energy was stressed by Olson.[9,10] Recently, Goodale et al., using catheterization of the coronary sinus in a limited number of patients, have shown that at adequate blood levels of glucose, pyruvate and lactate the aerobic combustion of these substances can account for 90 to 100 per cent of the simultaneous oxygen consumption of the heart.[11] However, work on the heart-lung preparation has indicated utilization of non-carbohydrate material by the heart. Cruickshank believes that under aglycemic conditions the isolated dog's heart primarily uses fat.[12] The isolated perfused frog's heart, on the other hand, is able to utilize amino acids.[13] Ruhl found that only 30 per cent of the total myocardial oxygen consumption of the isolated heart could be accounted for by the combustion of carbohydrates.[14]

The first report of this series is concerned with a study of the glucose, lactate and pyruvate metabolism of normal and failing hearts of fifty-two patients. Succeeding articles of this series will deal with the myocardial metabolism of amino acids, fat and ketone bodies.

METHODS

Blood from the coronary vein was obtained by direct intubation of the coronary sinus.[15–18] In twenty-five patients coronary blood flow per unit of left ventricular muscle was measured by the nitrous oxide method.[16] Blood glucose was determined by the method of Hagedorn and Jensen[19] using the method of Somogyi to prepare the blood filtrates.[20] Pyruvate was determined according to the method of Friedemann and Haugen, using a trichloracetic acid filtrate.[21] Lactate was measured by the method of Barker and Summerson.[22] The manometric

* From the Departments of Medicine and Physiology, Medical College of Alabama, Birmingham, Ala. Work supported by the U. S. Public Health Service, Grant #H-1129 (CS), the Life Insurance Medical Research Fund, and the Commonwealth Fund, New York, N. Y.

TABLE I

Patients without Heart Failure	Diagnosis	Cardiac Index /L./M²	Left Ventricular Work /Kg./min.	Respiratory Quotient Heart	Coronary Flow (cc./min. /100gm.)	Blood Levels and Myocardial Extractions							Myocardial Usage (100 gm.)				O_2 Extraction Ratio %			Conversion Factor		
						O_2 (vol. %)	Arterial Glucose (mg. %)	Glucose Extraction (mg. %)	Arterial Pyruvate (mg. %)	Pyruvate Extraction (mg. %)	Aterial Lactate (mg. %)	Lactate Extraction (mg. %)	O_2 (mg./min.)	Glucose (mg./min.)	Pyruvate (mg./min.)	Lactate (mg./min.)	Glucose	Pyruvate	Lactate	Glucose	Pyruvate	Lactate
1, R. B.	AV fistula	8.4	22.5	0.89	105	11	123	3.0	0.30	0.14	.....	....	11.6	3.15	0.147	....	20.45	0.81	.....	1.10	2.78	.....
2, W. R.	Rheumatic	2.75	5.6	....	80	10.2	110	7.0	1.75	0.20	13.0	1.0	8.2	5.6	0.160	0.80	51.47	1.2	7.35	0.12	4.67	0.76
3, C. T.	Thyrotoxic	5.3	15.5	0.59	65	12.1	115	8.0	2.40	0.25	28.0	8.0	7.9	5.2	0.163	5.2	49.6	1.32	49.5	0.31	11.74	0.31
4, A. M.	Hypertensive	3.16	8.9	0.42	111	8.1	134.5	6.5	2.08	0.23	17.8	5.3	8.99	7.2	0.255	5.8	60.1	1.8	49.0	0.15	4.94	0.18
5, M. D.	Rheumatic	3.0	6.1	0.31	.....	7.7	122.4	8.4	1.41	0.34	24.1	5.4	.....	.....	.....	....	81.8	2.82	5.25	0.07	2.16	1.16
6, W. M.	Hypertensive	4.1	13.9	0.72	80	11.8	95.3	10.3	1.07	0.31	9.5	3.3	9.4	8.2	0.248	2.64	65.5	1.68	20.9	0.21	8.27	0.67
7, R. J.	Normal	3.35	9.8	0.53	90	10	94	11.0	0.93	0.20	18.0	8.0	9.0	9.9	0.180	7.2	82.5	1.28	60	0.12	7.66	0.16
8, E. P.	Hypertensive	4.8	17.7	0.95	123	10	81	2.5	2.0	0.24	7.8	1.8	12.3	3.1	0.295	2.21	18.7	1.53	13.5	0.95	11.57	1.31
9, R. S.	Rheumatic	4.2	.....	0.63	.....	9.6	98	6.0	2.0	0.60	12.3	1.1	.....	.....	.....	....	47.0	4.0	8.6	....	.....	.....
10, N. K.	Normal	6.45	12.9	0.58	130	9.3	86	3.5	2.73	0.13	12.0	1.8	12.1	4.5	0.169	2.34	28.0	0.97	14.5	0.46	14.33	0.89
11, M. D.	Hypertensive	1.99	5.05	0.55	91	13.05	120	15.0	2.5	0.20	21.0	3.0	12.6	13.65	0.182	2.73	80.1	0.9	16.2	0.20	5.61	0.31
12, H. C.	Rheumatic	2.83	.....	0.15	.....	11.64	74	5.0	0.66	0.164	6.25	3.0	.....	.....	.....	.....	32.2	0.8	19.3	....	.....	.....
13, A. H.	Hypertensive	2.60	6.5	0.67	137	9.30	84	1.0	0.89	0.33	8.0	1.6	12.7	1.37	0.452	2.19	8.1	2.3	12.9	0.80	2.83	0.50
14, M. B.	Hypertensive	3.90	13.0	0.82	115	8.90	83	6.0	1.76	0.39	6.14	3.5	10.23	6.9	0.448	4.04	50.56	3.5	29.6	0.26	3.71	0.44
15, M. T.	Rheumatic	3.27	5.15	0.67	94	10.1	75	3.0	13.35	0.275	8.25	0.8	9.5	2.82	0.258	0.77	22.3	1.77	6.1	0.23	2.91	0.21
16, J. S.	Congenital	5.0	.....	0.94	.....	9.55	75.5	2.5	2.0	0.08	9.45	1.3	.....	.....	.....	....	19.6	0.53	10.2	....	.....	0.84
17, K. D.	Hypertensive	4.1	11.9	0.86	114	9 80	93	3.0	1.02	0.20	6.5	2.5	11.2	3.42	0.228	2.85	23.0	1.3	19.1	0.52	9.19	3.62
18, L. S.	Rheumatic	2.78	6.99	0.81	73.5	9.30	84	5.0	1.34	0.77	12.0	1.3	6.84	3.67	0.198	0.99	40.3	1.86	10.49	0.17	3.76	0.62
19, L. S.	Rheumatic	2.78	7.05	0.89	88.0	9.75	85	4.0	1.21	0.09	14.2	2.0	8.58	3.52	0.079	1.76	30.7	0.59	15.38	0.23	11.95	0.66
20, L. P.	Rheumatic	1.35	.....	0.72	.....	11.6	90	2.0	1.49	0.00	25.0	2.0	.....	.....	.....	.....	12.9	0	12.93	....	.....	0.46
21, H. F.	Hypertensive	3.18	9.7	0.55	78.6	11.0	83.0	4.0	1.49	0.30	12.9	1.9	8.64	3.14	0.2	1.49	27.28	1.74	13.0	0.36	5.57	.....
22, E. H.	Hypertensive	4.93	19.35	0.86	.....	10.1	83.7	4.7	2.34	0.44	.....	....	.....	.....	.....	....	34.9	2.79	.....	0.55	6.94	0.75
23, J. W.	Congenital	6.36	11.65	0.56	.....	9.9	77.0	2.0	1.78	0.50	4.2	0.65	.....	.....	.....	....	15.15	3.21	4.92	0.77	3.63	0.27
24, J. W.	Congenital	6.80	2.72	0.52	.....	10.15	77.0	3.0	1.78	0.55	4.2	1.28	.....	.....	.....	....	22.1	3.45	9.45	0.12	0.78	2.37
25, E. H.	Hypertensive	4.93	19.35	....	.....	10.1	83.7	4.7	2.34	0.44	.....	....	.....	.....	.....	....	34.8	2.79	.....	0.56	6.94	0.29
26, M. L.	Thyrotoxic	7.9	14.8	0.69	.....	11.3	87.6	7.1	0.74	0.17	7.9	3.7	.....	.....	.....	....	47.1	0.96	24.6	0.31	15.42	.....
27, M. V.	Normal	6.12	.....	0.94	.....	11.0	86.0	2.2	1.35	0.08	1.25	0.35	.....	.....	.....	....	15.0	0.45	2.39	....	.....	0.60
28, E. M.	Rheumatic	4.26	9.5	0.79	130	9.9	83.7	4.1	0.70	0	17.7	2.1	12.87	5.33	.....	2.73	31.1	0	15.95	0.31	3.38	0.24
29, S. S.	Congenital	5.30	4.12	0.74	.....	10.0	91.5	10.0	1.47	0.19	5.75	2.33	.....	.....	.....	....	75.0	1.22	17.5	0.06	1.09	19.94
30, Q. J.	Hypertensive	2.4	7.8	0.82	112	10.0	95.5	2.7	0.89	0	6.5	0.5	17.0	3.02	0	0.56	20.3	0	3.75	0.38	0	2.08
31, C. N.	AV fistula	.....	.....	....	206	4.1	84.5	0.90	1.47	0.27	1.97	0.56	10.23	1.86	0.55	1.16	16.3	4.22	10.2	....	.....	.....
32, M. S.	Thyrotoxic	8.4	19.6	0.82	.....	10.7	76.8	1.9	1.53	0.2	3.9	0.4	.....	.....	.....	....	13.4	1.19	2.8	1.41	.....	.....
33, W. H.	Rheumatic	9.0	19.7	0.40	.....	10.0	111.0	7.0	1.09	0.19	6.5	2.67	.....	.....	.....	....	52	1.2	.....	....	.....	.....
34, B. C.	Congenital	.....	.....	.....	.....	12.8	146.	6.3	1.12	0.16	10.35	2.83	.....	.....	.....	....	37	7.9	17.3	....	.....	.....
35, O. G.	Luetic HD	5.2	13.4	0.64	.....	11.2	111.	3.5	.....	.....	5.33	1.7	.....	.....	.....	....	31.1	....	11	0.44	.....	1.2
36, L. B.	Normal	4.9	7.1	0.99	.....	8.7	106.	1.0	.....	.....	15.1	4.05	.....	.....	.....	....	8.5	....	34	0.08	.....	0.21
37, E. H.	Hypertensive	4.25	14.5	0.88	.....	12.9	85.5	4.7	0.38	0.04	4.6	2.13	.....	.....	.....	....	27.2	0.2	12.4	0.53	72.	1.16
38, V. T.	Thyrotoxic	15.0	43.4	0.72	.....	10.3	90.7	2.0	0.49	0.07	9.2	0.16	.....	.....	.....	....	14	0.4	1.16	3.1	108.	37.4
39, C. I.	Rheumatic	5.16	11.7	2.5	.....	6.8	95.3	1.0	0.34	0.05	7.12	1.08	.....	.....	.....	....	11.1	0.47	12.4	....	.....	.....
40, A. E.	Congenital	.....	.....	0.64	.....	9.3	76.0	1.3	0.39	0.02	11.5	1.7	.....	.....	.....	....	10.5	0.12	5.6	....	.....	.....
41, W. W.	AV fistula	4.3	8.0	0.85	.....	11.8	82.6	5.1	0.42	0.05	13.95	4.5	.....	.....	.....	....	32.0	0.27	39.0	0.25	21.6	0.31
42, E. T.	Hypertensive	3.75	7.9	0.75	77	10.1	93.2	1.0	0.24	0.14	8.3	3.4	7.0	.....	0.17	2.6	7.4	0.88	25.5	1.7	8.9	0.31
43, W. W.	Cor pulmonale	3.93	7.8	0.80	.....	8.6	95.7	2.4	0.47	0.07	14.3	3.3	.....	.....	.....	....	21.	0.5	29.	0.38	.....	0.27

method of Van Slyke and Neill was used for blood oxygen analyses.[23] Mixed venous blood was obtained from the pulmonary artery or the right ventricle for calculation of the cardiac output by the Fick principle.[24] The pulse rate was obtained from electrocardiographic tracings recorded during the procedure. The stroke volume was calculated as the ratio of minute volume/heart rate. Blood pressures were obtained with a strain gauge by direct puncture of either brachial or femoral artery. Mean pressures were obtained by planimetric integration of the area under the pressure curve. Left ventricular work was calculated in kg. meter from the formula of Starling.[25] The myocardial usage of oxygen, lactate, glucose and pyruvate was obtained per 100 gm. of heart as the product of coronary flow/100 gm. of cardiac muscle times the respective oxygen, glucose, lactate or pyruvate extractions. The glucose, lactate and pyruvate oxygen extraction ratios were calculated as the ratios of the oxygen equivalent of glucose (0.75), pyruvate (0.64) and lactate (0.75) to the myocardial oxygen extraction; thus the oxygen extraction ratios represent the contribution of the aerobic catabolism of these substances to the total myocardial oxygen extraction. For example, if the glucose extraction by the heart is 8.9 mg. per cent, the oxygen equivalent is 6.68 cc. of oxygen. Consequently, if the oxygen extraction of the heart is 9.4 volumes per cent, the glucose oxygen extraction ratio equals 71 per cent. If the oxygen extraction of any of these metabolites is elevated, it may be assumed that a large proportion of the energy taken in by the heart in the form of oxygen is used in the aerobic metabolism of this substance. Conversely, if the oxygen extraction ratio of a substance is decreased, a smaller proportion of oxygen taken up by the heart is used in the aerobic metabolism of this compound.

In order to estimate the relative efficiency with which the oxidative energy derived from these metabolites was converted into cardiac work, the energy conversion factor was obtained with the formula: energy conversion of glucose, pyruvate or lactate =

$$\frac{\text{work of left ventricle/Kg. (meters)}}{\text{glucose or pyruvate or lactate oxygen extraction ratios (per cent)}}$$

This ratio represents only a comparative index of the contribution of oxidative energy derived from glucose, lactate or pyruvate to the useful work of the heart and is not a quantitative value. By nature of this calculation comparisons between the energy conversion factors of different metabolites are not possible. However, a lowering of the contribution factor signifies that a small proportion of the oxidative energy derived from this specific compound is converted into mechanical work. On the other hand, an elevation of the contribution factor suggests more effective conversion of oxidative energy derived from this substance into useful work.

Most tests were carried out with the patient in the postabsorptive state, or shortly after ingestion of a meal containing carbohydrates. No effort was made to determine quantitatively the carbohydrate intake prior to the test. In eight patients (E. M., Q. J., C. N., M. S., W. H., L. M., G. M. and W. A.) studies were carried out before and after infusion of a 10 per cent glucose solution. After control samples had been obtained, the infusion was begun. Simultaneous blood samples from the coronary sinus and a peripheral artery were obtained after one, two, three, six and nine minutes from the onset of the infusion. In all but two patients (W. A. and G. M.) this was followed by an injection of 5 cc. of a 50 per cent glucose solution. Further samples were then taken at three-minute intervals.

Of the fifty-two patients in whom these studies were performed nine were in cardiac failure. (Table II.) Of these three suffered from failure due to hypertensive or rheumatic heart disease. The cardiac index in these patients varied from 1.97 to 4.3 with an average of 2.78 L./M²/minute. Consequently, these patients were in low output failure. The remainder in this group had thyrotoxicosis with failure. In these individuals the cardiac index ranged from 4.7 to 7 L./M²/minute, with an average of 5.6 L./M²/minute; therefore, in these patients high output failure was present. Of the forty-three patients who were not in cardiac failure, several had no evidence of heart disease, others had hypertensive cardiovascular disease, rheumatic valvular disease, congenital heart disease, thyrotoxicosis, arteriovenous fistula or anemia. (Table I.)

RESULTS

Glucose Metabolism. Table I illustrates that the glucose extraction of the non-failing heart

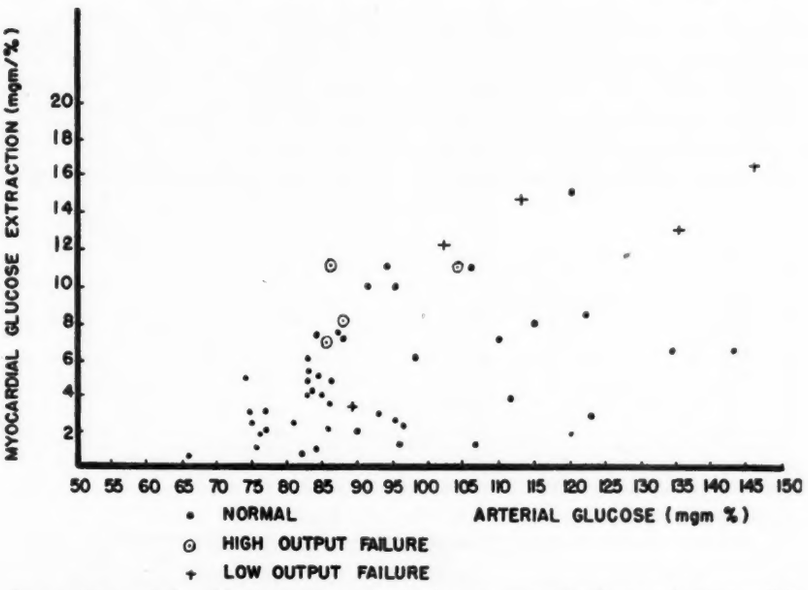

FIG. 1. The relationship between arterial glucose concentration and myocardial glucose extraction in individuals in the postabsorptive state or after the ingestion of a meal containing carbohydrates. At low arterial glucose concentrations the heart extracts only small amounts of glucose suggesting either breakdown of glycogen or combustion of substances other than glucose. The myocardial extraction rises as the arterial blood level increases, until at blood concentrations above 110 mg. per cent the extraction appears to have reached its maximal value.

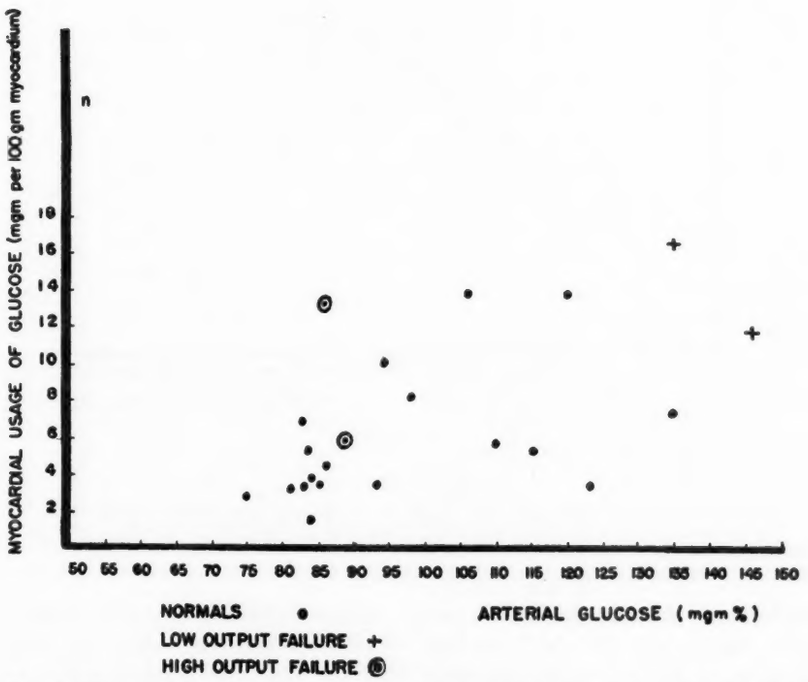

FIG. 2. The relationship between myocardial glucose usage and arterial glucose concentration is similar to that between arterial glucose concentration and myocardial glucose extraction outlined in Figure 1.

varied from 0.9 to 15.0 mg. per cent. The glucose consumption per 100 gm. of heart muscle varied from 1.37 to 13.65 mg./100 gm./heart/minute and the oxygen extraction ratios of glucose from 7.4 to 82.5 per cent. Average values for myocardial glucose extraction and consumption are not calculated since both glucose extraction and consumption are functions of the arterial glucose concentration. Figure 1 illustrates that at blood sugar concentrations of below 80 mg. per cent the coronary arteriovenous glucose difference was less than 4 mg. per cent. As the arterial glucose concentration increased, the extraction rose rapidly until at blood concentrations above 110 mg. per cent the extraction appeared to have reached its maximal value. (Fig. 1.)

Figure 2 illustrates that a similar relationship exists between arterial glucose concentration and myocardial usage of glucose. Evans also found that in the heart-lung preparation rising glucose concentrations in the perfusate resulted in increased myocardial glucose extraction.[5] The relationship between glucose extraction

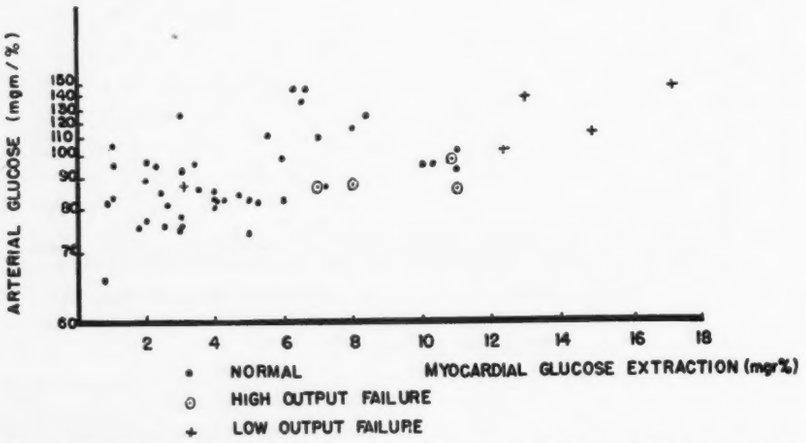

FIG. 3. The myocardial glucose extraction is a function of the logarithm of the arterial glucose concentration.

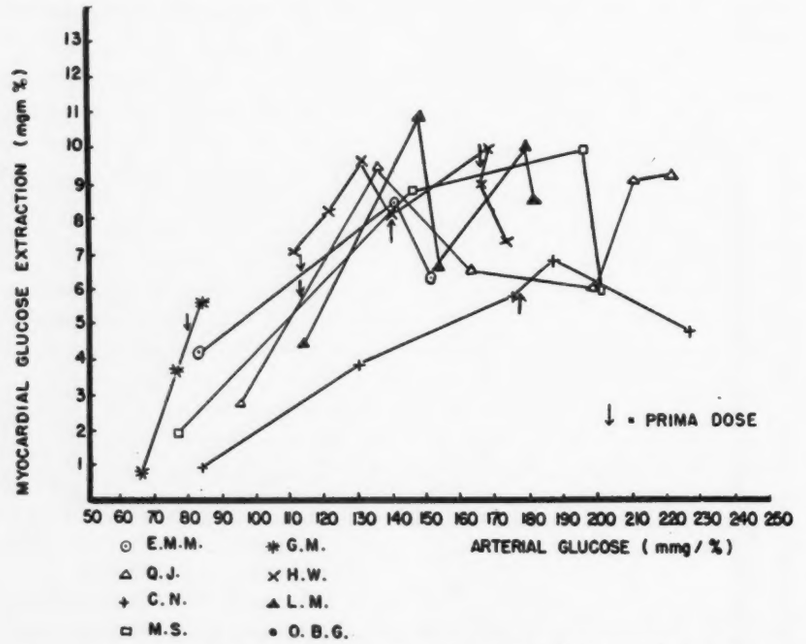

FIG. 4. Intravenous infusion of a 10 per cent glucose solution results in increasing myocardial glucose extraction regardless of the height of the arterial blood glucose concentration.

TABLE II

Heart Failure Patients	Diagnosis	Cardiac Index /L./M²	Left Ventricular Work /Kg./min.	Respiratory Quotient Heart	Coronary Flow (cc./min. /100gm.)	Blood Levels and Myocardial Extractions							Myocardial Usage (100 gm.)				O_2 Extraction Ratio %			Conversion Factor		
						O_2 (vol. %)	Arterial Glucose (mg. %)	Glucose Extraction (mg. %)	Arterial Pyruvate (mg. %)	Pyruvate Extraction (mg. %)	Arterial Lactate (mg. %)	Lactate Extraction (mg. %)	O_2 (mg./min.)	Glucose (mg./min.)	Pyruvate (mg./min.)	Lactate (mg./min.)	Glucose	Pyruvate	Lactate	Glucose	Pyruvate	Lactate
1, O. H.	Hypertensive	4.39	11.5	0.28	126	6.5	135	13	0.13	0.13	0	.....	8.19	16.4	0.16	.....	150	1.276	.....	0.07	8.98	.....
2, V. R.	Hypertensive	2.00	4.1	....	...	8.8	102	12.2	4.50	0.75	0	.....	.....	.....	.....	.....	103.7	5.45	.....	0.04	0.75	.....
3, N. R.	Pulmonary hypertrophy	1.97	4.85	0.90	...	11.7	113.1	14.8	1.90	0.25	21.75	5.65	.....	.....	.....	.....	94.87	1.36	36	0.05	3.57	0.13
4, R. W.	Rheumatic	4.25	.....	0.80	70	11.2	146	16.5	2.02	0.31	21.5	0.5	7.8	11.6	0.21	0.35	110.4	1.77	3.3	....	.....	....
5, C. F.	Thyrotoxic	4.48	14.1	0.76	96	10.6	88	8	1.21	0.13	9.75	3	10.2	7.68	0.12	2.88	56.6	0.8	21.2	0.25	17.63	0.67
6, W. C.	Thyrotoxic	4.70	11.5	0.60	125	12.0	106	11	1.19	0.66	20	9.2	15.0	13.75	0.82	11.5	68.7	3.51	54.5	0.17	3.27	0.44
7, E. M.	Thyrotoxic	6.28	21.7	0.82	119	12.45	86	11.0	1.02	0.15	4.0	1.0	14.8	13.09	0.18	1.19	66.2	0.77	6.0	0.33	28.18	....
8, M. L. L.	Thyrotoxic	7.9	9.52	0.69	...	11.3	87.6	7.1	0.74	0.17	7.9	3.7	.....	.....	.....	.....	47.1	0.96	24.42	0.20	0	0.59
9, F. B.	Hypertensive	3.24	7.63	0.90	...	8.3	88.6	3.1	0.54	0.08	9.34	0.99	.....	.....	.....	.....	28.0	0.60	9.0	0.27	12.7	0.85

and arterial glucose concentration appears to be a function of the logarithm of the arterial glucose concentration. (Fig. 3.)

In contrast to the results obtained either in the postabsorptive state or after ingestion of a carbohydrate meal, intravenous infusion or injection of a 10 per cent glucose solution resulted in increasing myocardial glucose extractions regardless of the height of the arterial blood glucose concentration. (Fig. 4.) When, following several minutes of glucose infusion, the arterial blood glucose level was further raised by the rapid intravenous injection of 5 cc. of a 50 per cent glucose solution, the myocardial glucose extraction showed a further increase. (Fig. 4.) The changes in glucose, lactate and pyruvate extraction, as well as their respective oxygen extraction ratios which resulted from intravenous infusion of glucose, are illustrated in Figure 5. It may be seen that a rise in arterial glucose concentration resulted in most instances in a slight increase in lactate absorption by the heart muscle. Furthermore, the contribution of the combined catabolism of glucose, lactate and pyruvate to the aerobic metabolism of the heart (the carbohydrate oxygen extraction ratio) more than doubled in the majority of these tests. (Fig. 5.) In two patients (C. N. and L. M.) the carbohydrate oxygen extraction ratios averaged more than 100 per cent. (Fig. 5.) The increased participation of carbohydrates in the aerobic metabolism

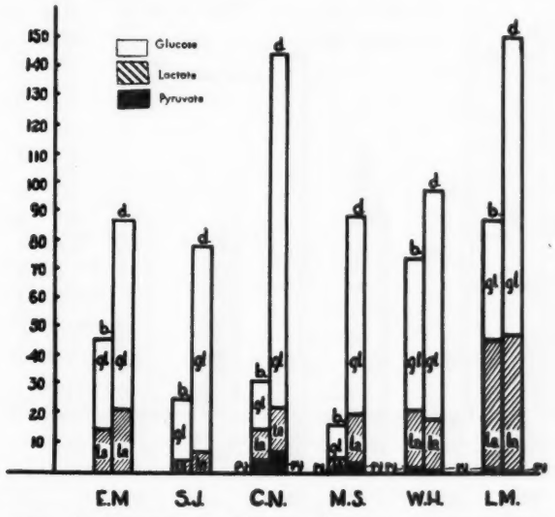

FIG. 5. Changes in glucose, lactate and pyruvate extraction and oxygen extraction ratios resulting from intravenous infusion of glucose. The carbohydrate oxygen extraction ratios increased in most of these tests.

of the heart probably indicates that the combustion of non-carbohydrate sources diminishes under these circumstances.

The results obtained on glucose metabolism in failure are illustrated in Table II and Figures 1, 2, 3, 6 and 7. In low output failure values for

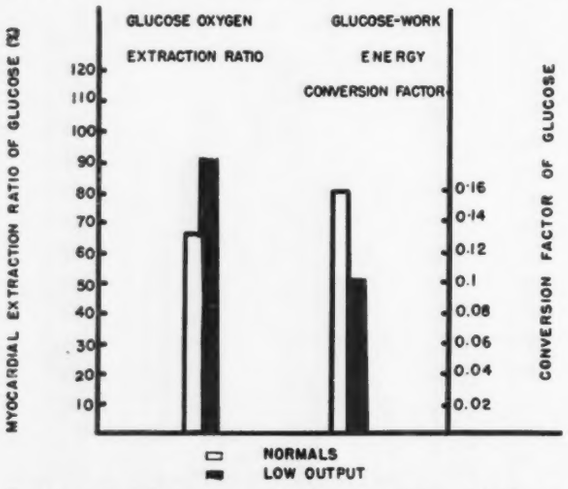

FIG. 6. Arterial glucose range between 110 and 146 mg. per cent. Comparison of the glucose oxygen extraction ratio and the glucose conversion factor in individuals without failure and in patients with low output failure. The average glucose extraction ratio in failure is increased and the average glucose energy conversion factor is diminished. This suggests a deficiency of the failing heart in converting chemical energy derived from glucose into useful work.

glucose extraction by the heart fall either within the range of data accumulated on non-failing hearts or appear to be above that range. (Table II.) A comparison of the glucose extraction ratio and the energy conversion factor of failing with normal hearts above arterial glucose levels of 110 mg. per cent is possible, since above this level there appears to be no more appreciable extraction of glucose. (Fig. 1.) Figure 6 illustrates that in low output failure the average glucose-oxygen extraction ratio was increased and the average glucose energy conversion factor diminished, indicating a deficiency of the failing heart to convert aerobic energy derived from glucose into useful work.

Table II indicates that in three of the four patients with high output failure studied the arterial glucose concentration varied little (from 85 to 90 mg. per cent). Consequently, a comparison between data obtained on these patients and those collected from individuals without heart failure in whom similar arterial glucose concentrations were found, was possible. Figure 7 shows an increase in glucose-oxygen extraction ratio and a decrease in the energy conversion factor, illustrating that in high output failure the heart is deficient in converting aerobic energy from glucose into useful work. (Fig. 7.)

Lactate Metabolism. The effect of rising arterial lactate concentrations on myocardial

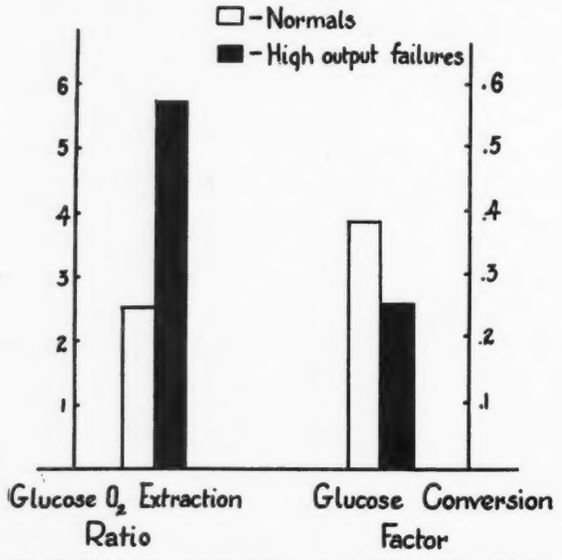

FIG. 7. In high output failure as in low output failure (Fig. 6) there is an increase in the glucose extraction ratio and a decrease in the glucose energy conversion factor.

lactate extraction and usage is illustrated in Figures 8 and 9. No effort was made in these tests to raise arterial lactate concentration by infusion of lactate. Rather, spontaneous variations in arterial lactate concentrations were correlated with lactate extraction and usage. The myocardial lactate extraction of the heart varied from .16 to 9.2 mg. per cent, the usage from 0.35 to 11.5 mg./100 gm./minute of heart muscle. (Table I.) It may be seen from Figure 10 that increases in arterial glucose concentration were accompanied with a rise in arterial lactate level. A rise in arterial lactate concentrations led to an increase in myocardial extraction and usage. (Figs. 8 and 9.) This finding is similar to that observed for glucose. (Figs. 1 and 2.) Myocardial lactate extraction was extremely small at arterial blood lactate concentrations from 0 to 12 mg. per cent. (Fig. 8.) As this value was exceeded there was a rapid rise in myocardial lactate extraction. (Fig. 8.)

As compared to glucose, however, myocardial lactate extraction and usage, as well as the lactate oxygen extraction ratio, were usually significantly lower. (Table I.) This is in contrast to Evans' findings on the heart *in vitro*, which

seemed to prefer lactate to glucose.[5] The relationship of the myocardial lactate extractions plotted against the logarithm of the arterial lactate concentrations follows a parabolic curve. (Fig. 11.)

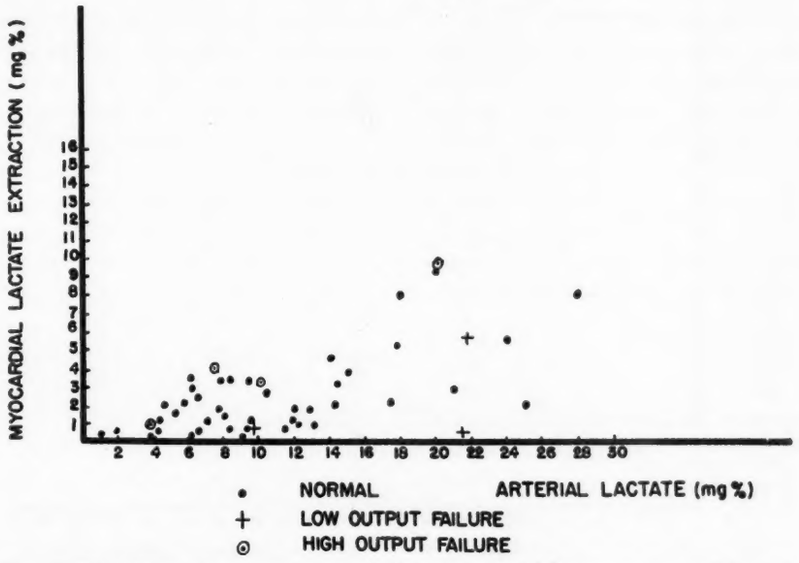

FIG. 8. The effect of spontaneous variations in arterial lactate concentration on the myocardial lactate extraction. A rise in arterial lactate concentration leads to increased myocardial lactate extraction.

A comparison between lactate values found in normal hearts and hearts in low output failure is not possible because of the considerable scatter of the data. (Table II.) However, a comparison of results obtained on non-failing hearts and hearts with high output failure was possible, since the majority of results were obtained at arterial lactate levels ranging from 2 to 10 mg. per cent where variations in myocardial lactate extractions are small. (Table II, Fig. 8.) Figure 12 illustrates that in these patients the contribution of aerobic catabolism of lactate to total myocardial oxygen extraction (the lactate oxygen extraction ratio) was considerably greater than in normal individuals. As a result the relative efficiency with which the oxidative energy derived from combustion of lactate was converted into cardiac work was diminished, despite the increase in cardiac work. (Table II, Fig. 12.)

Pyruvate Metabolism. The extraction and usage of pyruvate by the heart muscle was smaller than that of either glucose or lactate, with a range of from 0 to 0.77 mg. per cent and from 0 to 0.83 mg./100 gm. of heart muscle, respectively. (Table I.) No definite trend in the relationship between arterial pyruvate concentration and myocardial pyruvate extraction and usage could be detected. This may have been the result of analytic difficulties in determining small pyruvate coronary arteriovenous differences.

COMMENTS

Results reported in this paper deal with the extraction and usage of carbohydrates by the normal and failing human heart *in vivo*. From data thus obtained certain conclusions can be drawn as to the relative contribution of the catabolism of these substances to the over-all oxidative metabolism of the heart and on the conversion of oxidative energy derived from the catabolism of these substances into cardiac work. It must be stressed, however, that oxidation of carbohydrates to carbon dioxide and water for the provision of energy may not be the sole factor in determining the coronary arteriovenous difference of these compounds. For example, an increase in myocardial glucose extraction may be the result of conversion of this compound into glycogen. This is a strictly aerobic process, since the supply of energy-rich phosphate bonds in adenosinetriphosphate must be continuously replenished by oxidations. In this case the oxygen extracted from the coronary blood would be used for storage and not for chemical energy. Eventually, heart muscle glycogen may be used for the provision of energy but it is doubtful whether this would lead to the formation of

glucose.[26] Only the last portion of this breakdown is aerobic, since from glycogen through the formation of pyruvic acid the anaerobic path of carbohydrate metabolism must be the major pathway.

glycogen from which free energy may be available as the necessity arises ("kinetic stability"). At the same time there is no reason to except the heart muscle from the fate of other body tissues in which it has been shown that all tissue

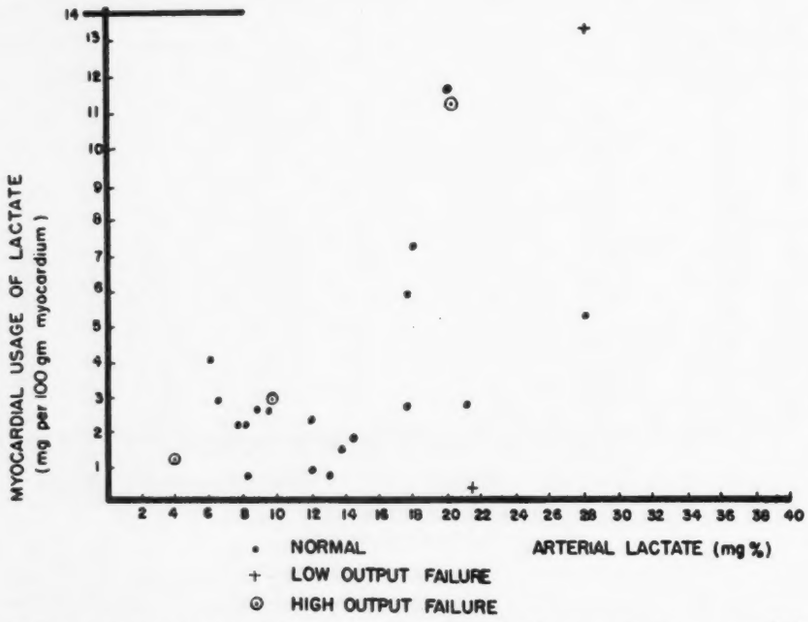

FIG. 9. Increased arterial lactate concentration leads to a rise in myocardial lactate usage.

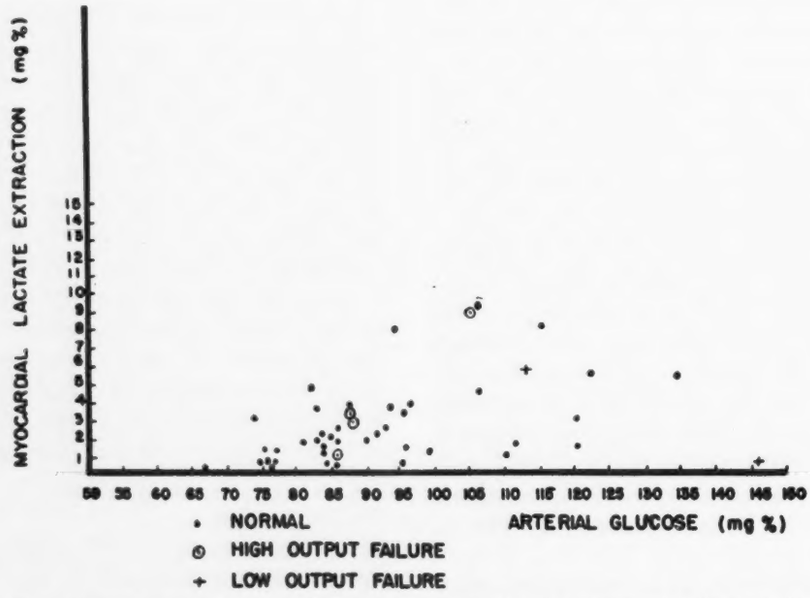

FIG. 10. An increase in arterial glucose concentration is accompanied by a rise in arterial lactate level.

It is probable that in the heart, as in other organs, there is present not only "kinetic stability" but also a "dynamic steady state."[27] Thus glucose may be stored in the form of components undergo continuous turnover in balance ("dynamic steady state"). It was considered that additional information as to the fuel burned by the heart might be obtained by

comparisons of its respiratory quotients but, although the respiratory quotients obtained are included in Tables I and II, it is unlikely that much additional information can be derived from them since the respiratory quotient even of single organs is a composite of many respiratory quotients arising from different chemical reactions occurring at the same time.[28] In brief, the methods described in this report do not permit of any conclusions as to the metabolic pathways within the heart muscle cell.

The results show that at low arterial glucose concentrations the myocardial glucose extraction, usage and oxygen extraction ratio are low; as the arterial glucose level rises following the ingestion of glucose, the myocardial extraction and usage increases. (Table I, Figs. 1 and 2.) Figure 1 illustrates that at blood concentrations of glucose exceeding 110 mg. per cent the glucose extraction has reached its maximal values. The relationship between glucose extraction and arterial glucose concentration is a function of the logarithm of the latter. (Fig. 3.) Small glucose oxygen extraction ratios at arterial blood concentrations suggest either breakdown of myocardial glycogen or combustion of substances other than glucose.

When the arterial blood glucose concentration is suddenly raised, as the result of intravenous infusions of glucose, an upper limit of glucose extraction appears to be absent. (Fig. 4.) It is likely that the heart, when confronted with a suddenly increased glucose load, uses sugar not only for oxidative processes but probably also for storage in the form of glycogen. It has been shown by Butsch that during intravenous infusions of glucose the amount of glycogen formed in the body from each increment diminishes but that glycogenesis does not diminish as rapidly as does oxidation.[29] As the quantity of glucose ingested increases, a relatively large proportion retained goes to form glycogen. It is likely that in the heart, too, both storage and combustion of carbohydrates vary directly with the blood sugar up to the limit of the myocardium to utilize sugar. This limit is fixed by the capacity to store sugar and by the total energy production.[30]

A rise in arterial lactate level is followed by an increase in myocardial lactate extraction and usage. (Figs. 9 and 10.) In this respect, at least, glucose and lactate appear to be handled by the myocardium in a similar fashion. Certain differences, however, are noticeable. In the first place the heart appears to prefer glucose to lactate. Even at high arterial lactate concentrations of from 24 to 28 mg. per cent, the myocardial glucose extraction exceeds that of lactate. (Patients C. T., M. D. and L. P., Table I.) The relationship between the blood level of lactate and its myocardial extraction also differs from that of glucose in this respect. The extraction of glucose appears to be a function of the logarithm of its arterial concentration (Fig. 3) while the myocardial lactate extractions plotted against the logarithm of the arterial lactate level follows a parabolic curve. (Fig. 11.) In general, however, the results on myocardial lactate extraction and usage confirm the conclusions obtained on the heart-lung preparation and on the amphibian heart, namely, that lactate can be utilized by the myocardium.[5,31] Therefore, the heart muscle can utilize lactate either for formation of glycogen or for direct provision of energy, in contrast to skeletal muscle in which lactic acid formation represents the dead-end of a metabolic pathway.

Because of the small coronary arteriovenous pyruvate differences no definite conclusions can be drawn as to the relationship between arterial pyruvate concentration and its myocardial extraction and usage. There is little doubt, however, that pyruvate is metabolized by the human heart, as suggested by Braun-Menendez,[8] Goodale,[11] Olson[9] and Miller and Olson.[10] The latter authors found that in heart muscle slices the utilization of pyruvate and lactate is a function of the initial concentration of substrate and that the rate of decline in the utilization of pyruvate is a logarithmic function of time.[10]

In the majority of patients the total aerobic metabolism of glucose, lactate and pyruvate combined still falls far short of the total oxygen consumption of the left ventricle. (Table I.) This is the case even in some patients with high arterial glucose concentration. This suggests that the myocardial oxygen consumption may be covered by aerobic catabolism of non-carbohydrate substances. It has been demonstrated in animal experiments that carbohydrates are not essential as fuel of muscular contraction and that the necessary energy can be provided from other foodstuffs.[32,33] Thus muscular activity continues in the depancreatized dog, supported by energy derived primarily from fat.[30] The human heart apparently also utilizes, or even prefers, non-carbohydrate sources as fuel.[34] This latter possibility is supported by findings

which indicate myocardial extraction and usage of amino acids, particularly fats and ketone bodies. This is in line with the observation recently stressed by Peters that the endogenous supply of carbohydrates, primarily in the form of glycogen, is used by the body with increasing

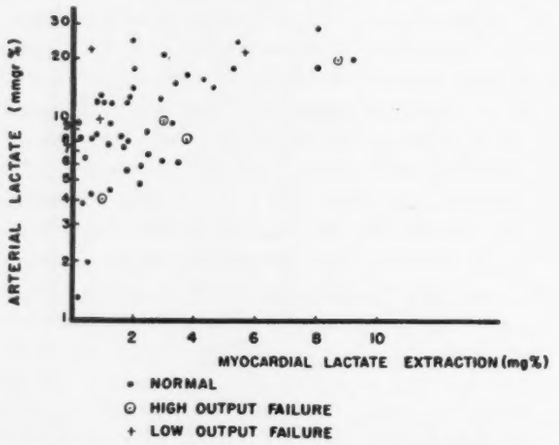

FIG. 11. The relationship of the myocardial lactate extraction plotted against the logarithm of the arterial lactate concentration appears to follow a parabolic curve.

economy as it becomes depleted. Thus after an overnight fast three-fifths of the energy production is sustained by fat.[35] The heart appears to be no exception.

Results obtained on the glucose metabolism of hearts in low and high output failure reveal the same general trend. (Table II, Figs. 6 and 7.) In the majority of patients in low and high output failure the myocardial glucose extraction and the glucose oxygen extraction ratio are elevated and the glucose conversion factor is diminished. (Figs. 6 and 7.) In high output failure the myocardial lactate extraction and oxygen extraction ratio are below values observed in individuals with non-failing hearts. (Fig. 12.) This results in a lowering of the lactate energy conversion factor. (Fig. 12.) It has been previously pointed out that the failing human heart *in vivo* has partially lost its ability to convert aerobic energy into useful work.[36] The findings described in this report suggest that the hyper- and hypokinetic heart in failure has also become deficient in converting the energy derived from the aerobic breakdown of glucose and lactate into mechanical work. It is not yet possible to explain the factors which are responsible for interruption of the link between chemical energy derived from the breakdown of certain metabolites and the work of the heart. On the basis of work on heart muscle proteins, it appears possible that in failure there are structural physical-chemical changes in the contractile proteins (actomyosin) of heart muscle.[37] If this be the case then the metabolic alterations observed in cardiac failure

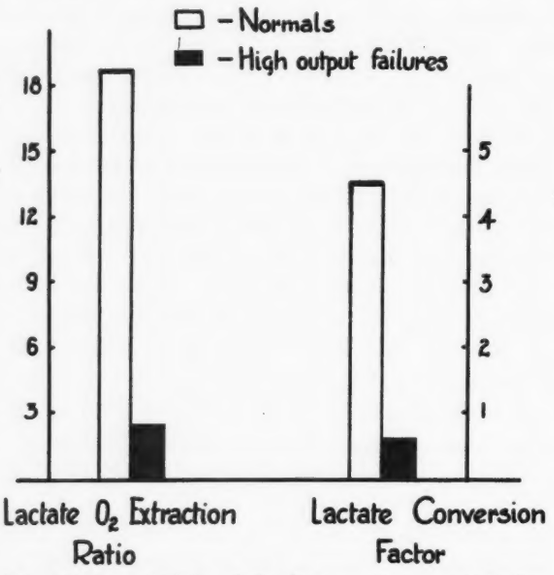

FIG. 12. Comparison of the lactate oxygen extraction ratio and the lactate conversion factor in individuals without failure and in patients with high output failure. The lactate conversion factor is diminished, suggesting deficiency in energy conversion of lactate.

are only the manifestation and not the underlying cause of the processes which lead to failure.

SUMMARY

The myocardial extraction and usage of glucose, lactate and pyruvate were measured in fifty-three patients with and without cardiac failure. The relative contribution of the catabolism of these substances to the oxidative metabolism of the heart (the oxygen extraction ratio) and the conversion of oxidative energy from these carbohydrates into cardiac work (the energy conversion factor) were estimated.

Usually, the total aerobic metabolism of glucose, lactate and pyruvate combined fell short of the total oxygen consumption of the heart. Consequently, the heart used for provision of energy either heart muscle glycogen or non-carbohydrate substances. The latter possibility appeared more likely.

Spontaneous rises in arterial glucose and lactate concentration were followed by an increase in their myocardial extraction and

usage. The myocardial extraction of glucose is a function of the logarithm of its arterial concentration while the myocardial lactate extractions plotted against the logarithm of the arterial lactate level followed a parabolic curve. At glucose blood concentrations above 110 mg. per cent no further uptake of glucose by the myocardium was noticeable.

When the arterial blood glucose concentration was suddenly raised, as the result of infusion, an upper limit of glucose extraction appeared to be absent. This might have resulted from glycogenesis as well as increased oxidation of glucose.

Pyruvate was utilized by the human heart.

In low and high output failure myocardial glucose and lactate extractions and the glucose and lactate oxygen extraction ratios were elevated; the glucose and lactate energy conversion factors were lowered. This indicates that the hyper- and hypokinetic heart in failure has become deficient in converting the energy derived from the aerobic breakdown of glucose and lactate into mechanical work.

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Postural Effects in Tetralogy of Fallot*

PAUL R. LURIE, M.D.
Indianapolis, Indiana

IN 1784 William Hunter[2] described with uncommon brilliance an autopsy-proven case of what many years later became known as tetralogy of Fallot. An excerpt from his paper follows: "Any hurry upon his spirits or brisk motion of his body would generally occasion a fit. And for some of the last years of his life he had found out by his own observation, that, when the fit was coming upon him, he could escape it altogether, or at least take considerably from its violence or duration, by instantly lying down upon the carpet, on his left side, and remaining immovably in that position for about ten minutes. I saw the experiment made with success."

Few other descriptions[3–5] of the symptoms of this disease detailed enough to include mention of posture were made through the years so that Taussig's abundant experience permitted her to contribute valuable new shading to the clinical picture in 1947.[6] She noted that these patients showed spontaneous preference for certain postures in which their cyanosis and dyspnea were minimized: the knee-chest position, sitting with the legs drawn up on the seat of the chair and squatting to relieve exertional dyspnea. The latter, being the most dramatic, has been mentioned in practically all editions of textbooks and review articles after 1947. The existence and importance of these postural effects is now unquestioned but their mechanism continues to be obscure. An explanation of this mechanism and its significance is the object of this paper.

MECHANISM

The present understanding of the hemodynamic consequences of the vertical stance of man[7] as it pertains to this problem can be summarized briefly. The effect of the upright posture in the normal individual is an increased filling of dependent blood vessels, especially veins, so that a decreased return of blood to the heart results and the cardiac output falls. But various reflexes maintain the arterial blood pressure by vasoconstriction and cardiac acceleration. It is only in an unusually prolonged and severe postural stress or in an exceptional individual with deficient reflexes that arterial hypotension occurs. Venous return against the stress of gravity is maintained, although usually at a reduced level, by several mechanisms; *vis a tergo*, the pumping action of skeletal and gastrointestinal musculature compressing veins equipped with valves, and the pumping action of breathing.

Some observations by others of patients with tetralogy of Fallot are of interest. Quantitative studies have shown that upon quiet standing the arterial oxygen saturation falls,[8,9] and that squatting reverses this.[9] Elastic bandages applied to the lower extremities obviate the need for squatting.[10] Hamilton and colleagues,[11] while studying a patient with this disease by cardiac catheterization, observed an instance of spontaneous syncope in the supine position. They noted a marked fall in systemic arterial pressure and a decrease in arterial oxygen saturation, which they attributed to an increase in venoarterial shunt, the right ventricular blood choosing the course of least resistance between the hypotensive aorta and the obstructed pulmonary artery. Precipitous decreases in arterial oxygen saturation were found in tetralogy patients during surgery when marked falls in systemic pressure occurred.[12] Varying the systemic pressure in a horizontal patient by the administration of tetraethylammonium halide and neosynephrine, however, failed to alter arterial saturation.[12]

Most of the speculation about the mechanism of postural effects in tetralogy has centered about the idea of a fall in systemic blood pressure causing an increase in venoarterial shunt.[10,11]

* From the Department of Pediatrics, Indiana University Medical Center; aided by grants from the James Whitcomb Riley Memorial Association and the Indiana Heart Foundation. Presented in part to the Central Society for Clinical Research, November 7, 1952.[1]

This concept implies that the postural reflexes maintaining arterial pressure are abnormal in tetralogy. On the other hand, no instance of clinical arterial hypotension in tetralogy had come under our observation. Although attacks of loss of consciousness are often seen in this disease, their course is only rarely, as in Hamilton's case,[11] suggestive of sudden arterial hypotension. Usually, cyanosis and dyspnea gradually increase and the loss of consciousness is properly ascribed to hypoxemia[13] and/or hypercapnea.

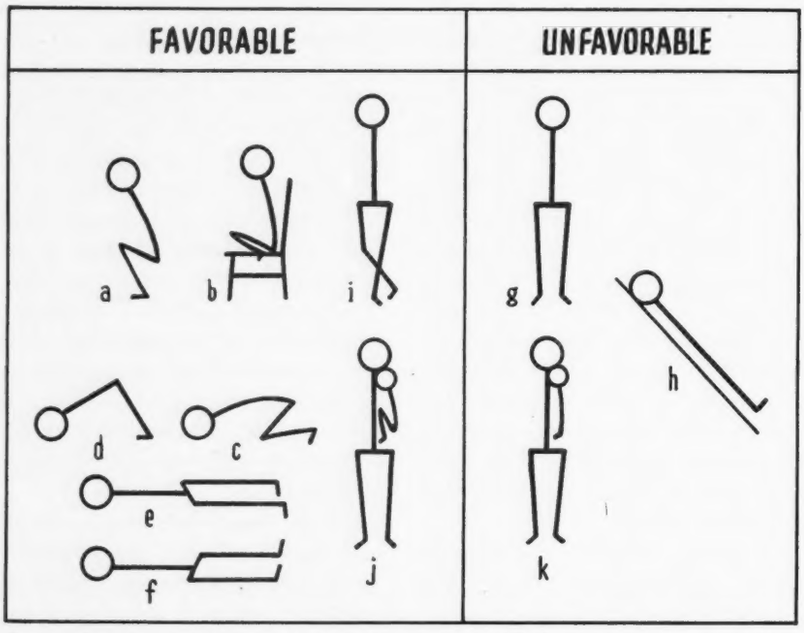

FIG. 1. Postures affecting patients with tetralogy of Fallot. *a*, squatting; *b*, sitting with legs drawn up on seat of chair; *c*, knee-chest; *d*, feet and head both on floor; *e*, prone; *f*, supine; *g*, quiet standing; *h*, foot-down tilt; *i*, protective crossing of the legs on quiet standing; *j*, infant held with knees pressed against abdomen; *k*, infant held with legs hanging down.

Present Studies

1. *Inspection of Postures; Suggestion of Relation between Volume of Venous Return and Comfort of Patient.* A variety of postures affect patients with tetralogy. A starting point in understanding the mechanism of these effects is to classify and examine the postures in search of a common factor. Reference to Figure 1 will aid in visualizing them. On the favorable side are: squatting (*a*), sitting with the legs drawn up on the seat of the chair (*b*), and the knee-chest position (*c*), as have been mentioned by Taussig.[6] We have observed two toddlers very happily assume a bizarre position of rest with the feet on the floor, bent over until the head also rests on the floor (*d*). Horizontal postures are all good, though prone (*e*) and lateral are distinctly better than supine (*f*). In the lateral positions the knees are usually drawn up. On the unfavorable side are quiet standing (*g*) and foot-down tilt (*h*). Patients asked to stand quietly, often cross the legs and squeeze them together (*j*), or stand quite restlessly, despite instructions. Babies can be soothed very well either in the knee-chest position or in the usual position in which babies are held against the parent's chest, with the notable exception that care must be taken to keep the baby's knees well squeezed into its abdomen, (*j* vs. *k*). One mother of a three-month old infant volunteered after discovering this: "His grandmother tells me that his legs won't grow if I hold him like that, but I find that it helps him."

Inspection of these postures reveals that the favorable positions are those which tend to minimize the effect of gravity upon venous return by compressing the venous reservoirs of the abdomen and lower extremities and/or bringing them as nearly as possible to heart level. The unfavorable postures permit blood to be pooled farther from the heart in regions where more work must be done against gravity to return it.

2. *Demonstration That Posture Alters Arterial Oxygen Saturation without Affecting Systemic Arterial Pressure.* The data in Table 1 confirm the observations of others[8,9] that quiet standing in this disease is associated with a fall in arterial oxygen saturation, and also shows this to be true in foot-down tilting. In each case the first determination of arterial saturation was a basal supine level and the second was taken two to five minutes after beginning of standing or tilt. On standing the saturations in all ten patients who were tested decreased 7 to 34 percentage points. Tilting to about 70 degrees produced decreases of 12 to 19 in the three patients so studied. In six of the cases the arterial blood pressure was also determined. When the patients were standing or tilted, the cuff was held at heart level. There were no significant decreases in blood pressure despite significant decreases in arterial saturation.

3. *Demonstration That Volume of Venous Return Is Correlated with the Arterial Oxygen Saturation.* As changes in venous return seemed involved in the changes in arterial saturation and arterial hypotension did not occur, it was of interest to test the effect upon arterial oxygen saturation* of various maneuvers which possessed in common the factor of varying venous return to the heart. The upper graph in Figure 2 shows a 15 point decrease in saturation upon standing two successive times identically reversed when the patient squatted and when he resumed the supine position. The lower graph shows the effect of tilting the same patient, which was similar to that of standing although slower. Its reversal by returning to the horizontal plane was prompt and like the reversal of the effect of standing by returning to the supine or the squatting position. Since squatting is most dramatically effective during the recovery from cyanosis and dyspnea which has been intensified by exercise, the comparison of the two curves in Figure 3 is illuminating. Although the subjects were two different individuals, they both started in the supine position, stood for one minute during which time saturation fell, then climbed up and down an 8-inch step for one minute, while saturation fell further. At the end of the exercise W. J. squatted, his saturation immediately started to rise and rose rapidly. This is the usual spontaneous behavior of a tetralogy patient in daily living. In contrast, E. H., upon request, remained standing at the conclusion of the exercise. Instead of recovering, this patient's saturation continued to fall precipitously and gradually levelled off at a low level. Immediately on lying down a rapid rise of saturation to the baseline occurred. This response is to be expected if venous return is involved because of the increased pooling of blood in leg muscles after exercise.[7]

TABLE 1

Patient	Age	Change in % Arterial Oxygen Saturation	Systolic Blood Pressure (mm. Hg)
		Quiet Standing	
E. H.	14	−14	95–100
A. B.	10	−8	110–110
S. G.	11	−33*	115–110
W. J.	6	−16	
R. H.	13	−16	
L. H.	3	−11	
J. S.	7	−7	
P. D.	10	−20	
J. M.	6	−8	
D. P.	3	−10	
		Tilting	
E. H.	14	−14	100–95
R. R.	20	−19*	115–115
W. J.	6	−12	105–110

* Determined by chemical analysis of arterial blood. Other values by Waters Conley oximeter.

The upper half of Figure 4 shows, in a patient with an arterial cannula, tilted three times to 70 degrees, feet down, for four minutes each, that the control fall in saturation of 20 percentage points was reduced to 13 points by application of elastic bandages to the abdomen and to only 4 points by additional bandages around the lower extremities. The bandages were not tight enough to affect the arterial blood pressure directly and it remained unchanged. Sufficient pressure was exerted by the bandages to reduce significantly the distensibility of the veins of the lower extremities and abdomen. In two cases, of which the lower curve in Figure 4 is an example, broad belts tightly applied to the abdomen slowed the increase of cyanosis on quiet standing. The rapid fall on standing without the belt can be contrasted to the slow fall with the belt. An increase in saturation was noted while supine after the belt was applied. The other of these

* Unless otherwise specified arterial oxygen saturation was measured with a Waters Conley ear oximeter.

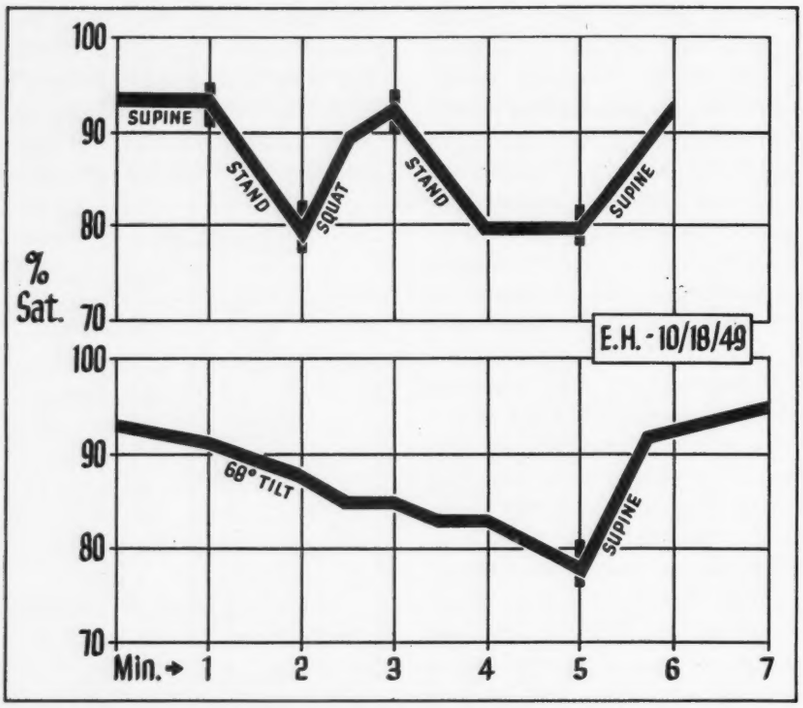

FIG. 2. Standing and tilting were associated with fall in arterial oxygen saturation, similar in degree, although the latter was slower. Reversed in both cases promptly by squatting or becoming supine.

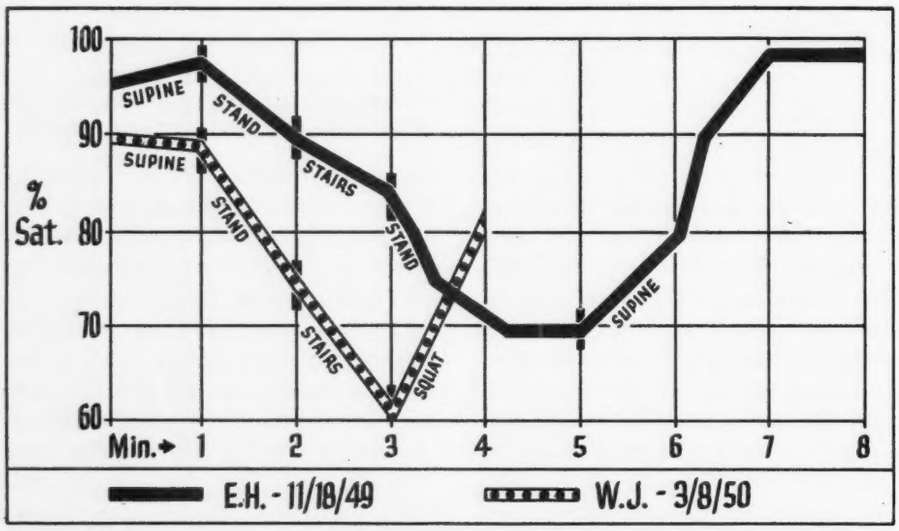

FIG. 3. After leg exercise arterial oxygen saturation continued to fall when patient remained standing, started to recover instantaneously with assumption of a favorable posture, whether the latter was delayed or immediate.

belt patients was a two year old boy who refused to submit to oximetry. This boy had never before in his life remained standing for more than one-half minute. With the belt he stood for nine minutes. Again it seemed likely that the belt compressed the abdominal veins, counteracting decreased venous return to the heart.

4. *Hemodynamic Study of a Case Showing the Mode of Influence of Volume of Venous Return upon Arterial Oxygen Saturation.* The following experiment illustrates the mechanism by which the

venous return to the heart influences arterial oxygen in tetralogy. Because of certain assumptions it cannot be considered a complete proof. An unusually calm, cooperative twenty year old male patient with tetralogy who had previously experienced the effects of various degrees of tilting was submitted to cardiac catheterization.* With the catheter in the right ventricular outflow tract and an indwelling brachial artery cannula, successive cardiac output estimations were made in 0, 20, 45 and 70 degrees of foot-down tilt. As there was only one catheter which was not moved and therefore only a single right heart sample in each position, it was assumed that there was no left to right shunt in the ventricle. This, although not more than 50 per cent probable in unselected cases of tetralogy,† was at least quite possible and did permit the calculation of both systemic and pulmonary artery flow in each position, using the blood oxygen content data illustrated in Figure 5 and the oxygen consumption data shown in Table II.

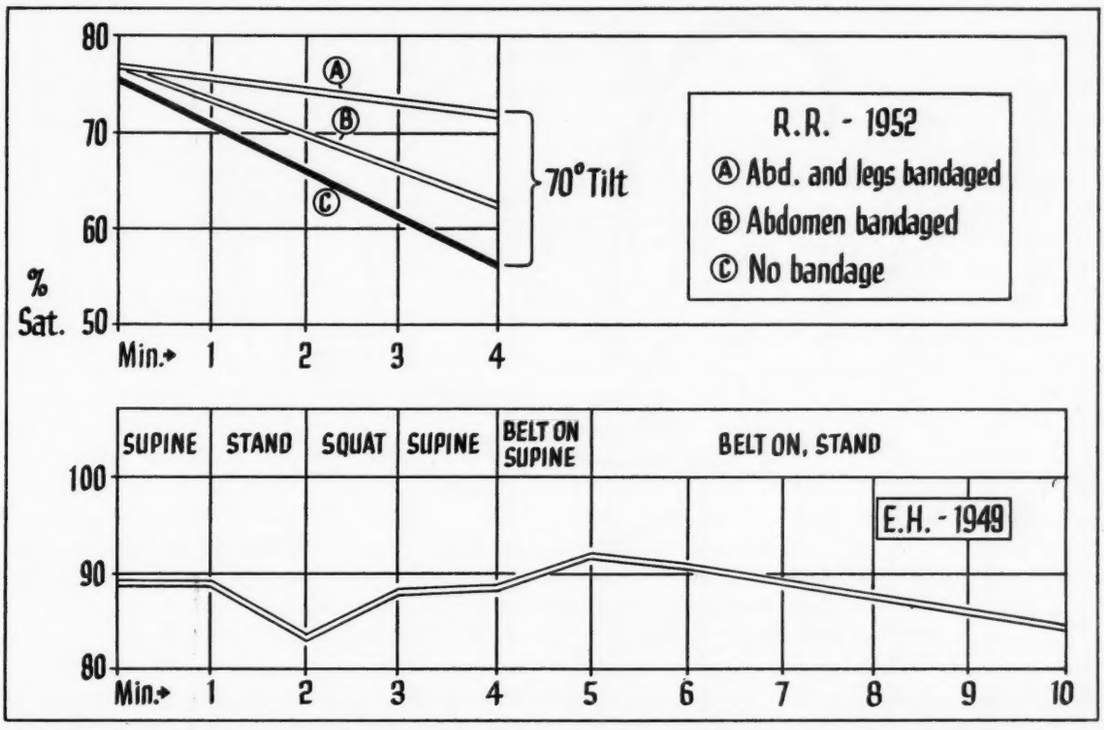

FIG. 4. Upper graph: In a patient with an arterial cannula, tilted three times, the control fall in arterial oxygen saturation of 20 per cent was reduced to 13 per cent by application of elastic bandages to the abdomen and to 4 per cent by additional bandages around the lower extremities. Lower graph: A broad abdominal belt slowed the decrease of arterial oxygen saturation on quiet standing.

From zero through 45 degrees the patient remained subjectively comfortable although his cyanosis visibly increased. The arterial saturation fell markedly. Oxygen consumed fell

* The methods used in this catheterization have been adequately described elsewhere,[14] except for certain small modifications: The value for pulmonary vein blood oxygen content was assumed to be constant at 95 per cent of the oxygen capacity. The pressures were measured with two Hathaway manometers. The pressure sensitive head of the manometer for right ventricular pressure was attached through a three-way stopcock to the hub of the catheter. Zero readings were taken in each different tilt by opening to air and later correcting for hydrostatic pressure by use of a spirit level, plumb line measurement of the vertical distance between the pressure head and the phlebostatic axis of Burch.[15] The right brachial artery cannula was connected through 15 cm. of polythene tubing to a three-way stopcock to which was attached the pressure head. Similar zero readings and hydrostatic pressure corrections were made at this point. Between samplings and pressure readings both systems were kept open with slow infusions of heparinized saline.

The blood samples were taken from catheter and cannula within thirty seconds of each other after a four-minute period in each position. The expired air sample was taken during the same minute in which the blood samples were taken.

Calculations of systemic flow,[16] pulmonary artery flow[16] and per cent of venoarterial shunt[17] were made by accepted methods.

† Based upon forty cases from two sources.[14,18]

very slightly with each tilt probably due to a delay in reaching an equilibrium before the sampling was done. Presumably, if sufficient time had been allowed for pulmonary perfusion by stagnating venous blood, the total body oxygen consumption was unchanged and would have so been registered in the expired air. At the same time, pulmonary ventilation increased, undoubtedly due to the stimulus of elevated blood carbon dioxide coincident with the decreased blood oxygen. The oxygen utilization per volume of pulmonary ventilation fell in a way typical of tetralogy of Fallot when patients are subjected to active muscular exercise, indicative in this disease of perfusion of the lungs lagging behind their ventilation.[18] The fall in venous return produced by posture was indicated by the fall in systemic flow. While the pulmonary artery flow was much smaller than the systemic flow, their ratio remained unchanged, and the computed percentage venoarterial shunt was remarkably constant. The constancy of the mean arterial pressures was remarkable. Thus reflex maintenance of arterial blood pressure was intact in spite of a marked reduction in venous return.

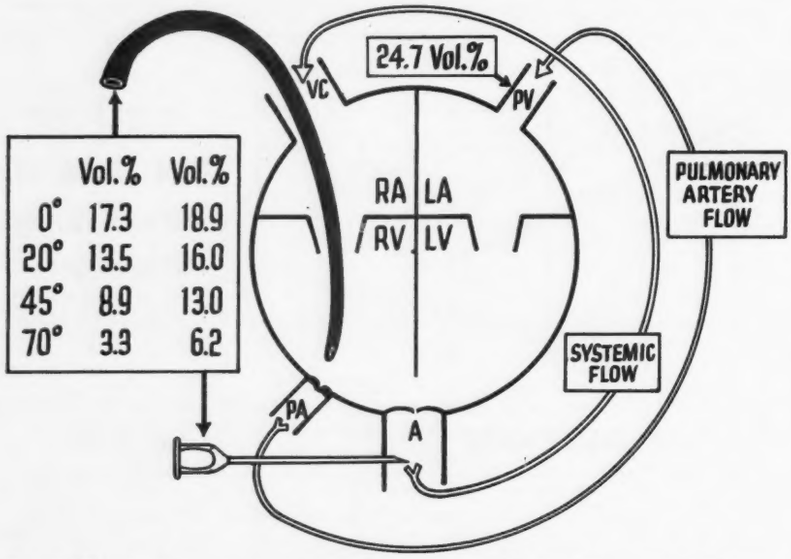

FIG. 5. Blood oxygen content of samples from catheter in right ventricular outflow tract and cannula in right brachial artery in patient with tetralogy of Fallot during tilting. (Pulmonary vein value was calculated and assumed constant.)

TABLE II

	Horizontal	20°	45°	70°
A. Observed Data				
Oxygen consumed, cc./min.	175	169	152	192
Breathing volume, L./min.	5.2	6.3	7.5	24.2
Pulse rate	84	84	102	126
Right brachial artery, mean pressure, mm. Hg	105	109	103	103
B. Derived Data				
Arterial oxygen saturation, %	72	61	50	24
Oxygen consumed, cc./L. of ventilation	33.7	26.8	20.3	7.9
Systemic flow index, L./min./M²	6.9	4.4	2.4	4.3
Pulmonary artery flow index, L./min./M.²	1.54	.99	.63	.59
Pulmonary artery flow/systemic flow	.22	.21	.25	.13
Venoarterial shunt, %	78	78	74	87

The changes occurring at 70 degrees of tilt could no longer be considered part of the controlled experiment as the patient, previously comfortable, became at this point violently dyspneic, as evidenced by the huge increase in pulmonary ventilation. This hyperventilation and marked general restlessness caused increased oxygen consumption and increased systemic flow due to increased venous return. This time the pulmonary artery flow did not increase so that a true change in per cent shunt did occur, but under conditions so complicated that it is of much less significance than the constancy of

shunt found with the better tolerated degrees of tilt. When the per cent shunt finally did increase, it was not as a result of a fall in arterial blood pressure.

The patient lost consciousness for a few seconds at the end of the 70-degree period. Comparison of this period with the 45-degree period, when the patient was mentally clear and unperturbed, shows that unconsciousness occurred with a similar arterial pressure, a higher systemic flow, but a much lower arterial oxygen. Thus in this instance, at least, it is possible to conclude that loss of consciousness was due to the brain being supplied with an adequate flow of blood containing too little oxygen and/or too much carbon dioxide.

In summary, then, within well tolerated limits tilting produced a fall in venous return and a fall in arterial oxygen saturation with no arterial hypotension and no change in percent venoarterial shunt.

This experiment illustrates the simple mechanism which appears to underlie all the postural effects in tetralogy of Fallot: A posture which reduces venous return while systemic oxygen extraction is maintained causes the returning venous blood to contain a lower concentration of oxygen. This less saturated systemic venous blood, mixing with saturated pulmonary venous blood, yields a resulting arterial mixture of lower saturation. In the same way a change of posture which increases venous return reverses this chain of events. While systemic arterial hypotension and alterations in the per cent of venoarterial shunt may both play a part under extraordinary circumstances such as actual hypotensive syncope, it is unnecessary to postulate that they are usually involved in the cyanosis and discomfort of adverse postures or the spontaneous preferences for the favorable positions.

Comment

The direct relationship between volume of venous return and level of arterial oxygen saturation in the presence of a venoarterial shunt has been demonstrated. This does not suffice to explain the difference in response to postures which should alter venous return, between tetralogy of Fallot and other diseases of the heart and lungs in which there is a venoarterial shunt. Patients with these other conditions have no immunity to the effects of gravity. Nor should it be necessary to postulate any hitherto unrecognized alterations in venomotor tone or other peripheral property of tetralogy of Fallot in distinction to these other diseases. As far as the peripheral effects of chronic tissue anoxia are concerned, such manifestations as clubbing of the digits are shared by all other types of severe cyanotic heart disease while the postural effects under discussion are not. The difference in response should be traceable to distinctions in the known clinical and physiologic characteristics of the diseases under consideration. Tetralogy of Fallot is notable for: (1) under basal conditions, reduced blood flow to the lungs, co-existing with a high systemic blood flow[18] and (2) rarity of congestive heart failure.[6]

The maintenance of systemic flow depends upon propulsion of blood from the heart and return of blood from the capillaries. The former is well handled in tetralogy of Fallot with its two heavy-walled systemic ventricles. If the latter is impaired, the systemic flow will fall below its normally high basal level, as illustrated in our catheterization study. We believe that reduced blood flow to the lungs, such as is produced by pulmonic stenosis, can in itself impair venous return in several ways so as to make postural effects evident in this disease in contrast to others with ample pulmonary blood supply.

In the normal individual whose blood is returned to the thorax against gravity the pulmonary circulation can be presumed to have a "storage" function, and probably regulatory[19] and pumping[20] functions. By "storage" we refer in this context particularly to the fact that the influence of gravity upon return from the pulmonary circuit is negligible in any position, the left auricle being near the center of the well concentrated pulmonary vascular bed. Thus blood which is brought back from the legs to the chest and pumped into the lungs is for a time protected from reexposure to the influence of gravity. To illustrate, given a normal individual with a systemic and a pulmonary artery flow of 5 L. per minute each, let us assume that, when tilted passively, half of his systemic flow passes to regions whence it must be returned against a significant pull of gravity. In contrast, a patient with tetralogy of Fallot might have a pulmonary artery flow of 2.5 L. per minute and a systemic flow of 7.5 L. With similar peripheral conditions half of this 7.5 L. is at once subjected to gravity. In short, the smaller the proportion of the returned venous blood that remains in the chest, the greater will be the influence of posture.

(In this illustration we have not attempted to show quantitatively how a resulting fall in venous return would in turn further reduce cardiac output.)

It is not definitely established to what extent in the normal individual respiratory changes in capacity[20] of the pulmonary vascular bed are present. If they do occur, and it is highly likely that they do especially with deeper breathing, it is reasonable to believe that they constitute a pumping mechanism aiding venous return which would be denied to an important degree to the patient with tetralogy or any other entity in which there was an anatomical obstruction to pulmonary blood flow. The universally accepted pumping effect of respiratory movement, that upon the right auricle and intrathoracic great veins, would be present in tetralogy but rendered ineffective to the extent of failure of the "storage" function of the pulmonary circuit discussed above.

Congestive heart failure is a rarity in uncomplicated tetralogy of Fallot. The orthopneic posture is conspicuous by its absence.[6] In contrast, patients with most other varieties of cyanotic congenital cardiac disease have, at least late in their course, congestive failure and are benefitted by having the chest and head elevated. This whole group of patients likely to go into failure should be divided into two classes in reference to the present problem, i.e., (1) those with abundant pulmonary blood supply under high pressure and (2) those with anatomically reduced pulmonary blood supply. Examples of Class 1 are transposition of the great vessels, complete and partial, Eisenmenger's complex and those cases of truncus and pseudotruncus arteriosus with adequate caliber of the vessels supplying the lungs. Class 2 is exemplified by pulmonic stenosis with patent foramen ovale or atrial septal defect and intact ventricular septum. In this class the shunt, if any, is from left to right unless the right ventricular pressure rises sufficiently to cause an elevation of right auricular pressure exceeding that in the left auricle. At this point right to left shunt begins. The patients in this class with mild venoarterial shunt are always near the borderline of congestive failure, and those with severe arterial unsaturation are in frank congestive failure.

There are two ways in which the presence of congestive heart failure would seem incompatible with the coexistence of the type of postural responses seen in tetralogy of Fallot. First, the systemic flow is low in congestive failure, except when anemia, hyperthyroidism or beri-beri are the cause, and the low cardiac output of congestive failure has been found to be not modified by changes in posture,[21] such as tilting, which affect cardiac output in the absence of congestive failure. This is probably due to the presence of more than adequate venous filling of an overstretched heart in any position. Secondly, the beneficial effect of the orthopneic posture, although complex, is due in part to improvement of pulmonary function by the gravitational shifting of fluid out of the thorax.[22] Indeed, the patient with congestive failure often is helped by keeping his legs dependent, a position unfavorable to the tetralogy patient. While lowness and unmodifiability of cardiac output may affect patients in both Classes (1) and (2), the second feature, proneness to pulmonary engorgement, applies only to Class 1. Indeed, it probably applies to these patients whether their engorgement due to the anatomical lesion has reached the point of clinical failure with pulmonary edema or not. The failure of normal pulmonary oxygenation in congenital lesions with marked left to right shunts[23] may be due to subclinical pulmonary edema. We have demonstrated[24] an *increase* in arterial saturation in a case of Eisenmenger's complex without obvious congestive failure as he was progressively tilted from horizontal to 45 degrees, foot down, but were unable to study him simultaneously for changes in adequacy of pulmonary oxygenation.

Our explanation of the mechanism of postural effects in tetralogy of Fallot has necessarily ended speculatively one dimension farther on in the highly complex fields of congestive failure and cardiopulmonary interrelationships.

SIGNIFICANCE

Diagnostic. The question of clinical specificity of these postural effects for tetralogy of Fallot cannot be answered categorically. Certainly there are few exceptions to the general rule that people who display these phenomena are helped by systemic to pulmonary anastomosis and its corollary that systemic to pulmonary anastomosis should be planned only after thorough diagnostic study and with a guarded prognosis in patients who do not have these characteristics. Reference is often made to a "history of squatting" as a requirement for this operation. It

should be better stated as a "demonstration of squatting." Insistent history taking can show that most well children have squatted at some time, as it is such a convenient posture. Indeed, many peoples of the world spend most of their non-walking, non-reclining hours in some form of squat. The simple test of leg exercise to the limit of tolerance, remaining standing on request with no relief of dyspnea or cyanosis, followed by squatting with immediate improvement, is far more convincing than any amount of history-taking. In the infant the rapid relief of dyspnea and improvement in color and irritability when he is placed in the knee-chest position or held with the knees firmly pressed into the abdomen are reliable diagnostic signs.

There are several other clinical conditions which behave similarly to tetralogy as regards the effect of posture. Certain cases of truncus and pseudotruncus arteriosus in which the caliber of the vessels supplying blood to the lungs is very small embody conditions similar to that in tetralogy, namely, high systemic flow, low pulmonary flow and absence of cardiac failure. Certain cases of tricuspid atresia as well as single ventricle with rudimentary outflow chamber into the pulmonary artery share these physiologic similarities. In all of these the principal difference from tetralogy of Fallot is one of cardiac contour. The preoperative symptomatology and the good effect of systemic to pulmonary anastomosis are similar.

Following surgical treatment by anastomosis, along with the relief of cyanosis and dyspnea comes a disappearance of postural effects. Most patients rarely need to squat. Postural effects are useful in diagnosis of the unsuccessfully operated patient, indicating, if persistent, that a larger anastomosis could be used. If postural effects have disappeared and dyspnea persists, the presence of cardiac failure should be suspected and a warning sounded against further systemic to pulmonary anastomosis.

Therapeutic. The various postural methods of producing the maximum venous return have been mentioned. That these are not mere curiosities is attested by many clinicians as well as the parents upon whom lies the tremendous nursing burden of tiding these children over until a suitable time for surgery is at hand. We have heard many older patients tell us how much easier they get their breath in the various positions under discussion.

In the case of infants it is especially necessary to discuss these postures carefully with the parents and nurses, actually demonstrating in minute detail all of the advantageous and disadvantageous postures. Often infants with tetralogy are placed in a bassinette in foot-down tilt in the conscious but misguided effort to relieve orthopnea, the expected cardiac symptom. The failure to do well in the knee-chest or lateral decubitus with the knees drawn up, of course, suggests the diagnosis of some other condition and does indicate trial of the orthopneic posture.

The use of a tight abdominal binder and elastic bandages to the lower extremities for short play periods by an infant with tetralogy trying to learn to walk might be justifiable. We have had little experience with such aids and have found that the milder patients do quite well with frequent squatting while the more severe cases have of necessity come to surgery before the toddling age. There may be some risk of loss of development of normal vasomotor reflexes from prolonged use of binders and bandages.

SUMMARY

The postural effects upon cyanosis and dyspnea in tetralogy of Fallot, including the beneficial effects of squatting, the knee-chest and other positions, and the disadvantageous effect of standing are shown to be directly due to alterations in volume of venous return with consequent change in the oxygen saturation of mixed venous blood. Speculations are adduced to explain the peculiarly marked effect of altered venous return in malformations when there is venoarterial shunt, reduced pulmonary blood flow coexisting with high systemic flow and absence of a tendency to go into congestive heart failure. Diagnostically, these postural effects are important when they can be demonstrated in the form of simple clinical tests. A patient demonstrating them will respond well to systemic-pulmonary anastomosis. Therapeutically, they are of real importance in carrying a patient through the period of waiting for definitive surgery.

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Venous Blood Flow during the Valsalva Experiment Including Some Clinical Applications*

SAMUEL CANDEL, M.D. *and* DAVID E. EHRLICH, M.D.
Brooklyn, New York

While a good deal has been written about the Valsalva experiment in regard to its effect upon intrathoracic contents, upon arterial, venous, intrapulmonary, intrapleural and intra-abdominal pressures, and upon venous flow through the vertebral system of veins,[1–7] no direct visualization of venous blood flow during the Valsalva experiment apparently has been attempted in man. It seemed to us that it would be of value to study the effect of the Valsalva experiment (forced expiration with a closed glottis, after a full inspiration) upon venous blood flow by direct visualization.

Fifty-two patients with normal cardiovascular systems were studied. Twenty cc. of a radiopaque solution was injected into a vein (cephalic or basilic) in the antecubital fossa and a venogram was obtained by x-ray. In each patient two studies were carried out consecutively. The first, which served as a control, was performed at the end of quiet inspiration, at which time the intrathoracic pressure was within normal range. Through the same needle (15 gauge), in the same vein, 20 cc. of the radiopaque solution was again injected while the patient was performing a Valsalva experiment, and another film was exposed.

The respiratory movements of the chest have a significant effect upon the movement of blood, derived from the viscera and the extremities, within the large veins of the thorax and the abdomen. During inspiration, when the ribs expand and the diaphragm descends, the intrathoracic pressure is about −6 mm. of Hg (81 mm. of water).[8] With expiration, when the ribs contract and the diaphragm ascends, the intrathoracic pressure rises to −2.5 mm. of Hg (34 mm. of water). Since there is a positive pressure of about 5 mm. water in the great veins at the level of their entrance into the right auricle, the flow of blood toward the heart is furthered by the positive pressure in the venous system and is aided by the suction pressure exerted by the thorax. The effective venous pressure would then be the sum of these two pressures which are acting in the same direction. Thus the effective venous pressure during inspiration would be 5 mm. of water plus 81 mm. of water, or a total 86 mm. of water. During expiration the effective venous pressure would be 5 mm. of water plus 34 mm. of water, or a total of 39 mm. of water. Therefore, during normal inspiration when the effective venous pressure is highest, the blood flow into the right auricle is greatest.

Exaggerated respiratory effects upon venous pressure may be produced during forced expiration with the glottis closed (Valsalva experiment). Under this condition the normally negative intrathoracic pressure may be converted into a highly positive pressure. This positive intrathoracic pressure, acting in a direction opposite to the intravenous pressure, becomes high enough to exceed the pressure in the veins within the thorax. The result of this is virtually to obstruct the return flow of blood into the thorax. The peripheral venous pressure may rise to 400 mm. of water.[8] It has even reached 700 mm. of water.[4,9] During the Valsalva experiment the effect of the impediment of venous flow into the thorax may be observed in the marked distention of veins of the face, neck, thora[4] and extremities. Venous

* From the Department of Medicine and the Department of Radiology, Veterans Administration, Brooklyn Regional Office.

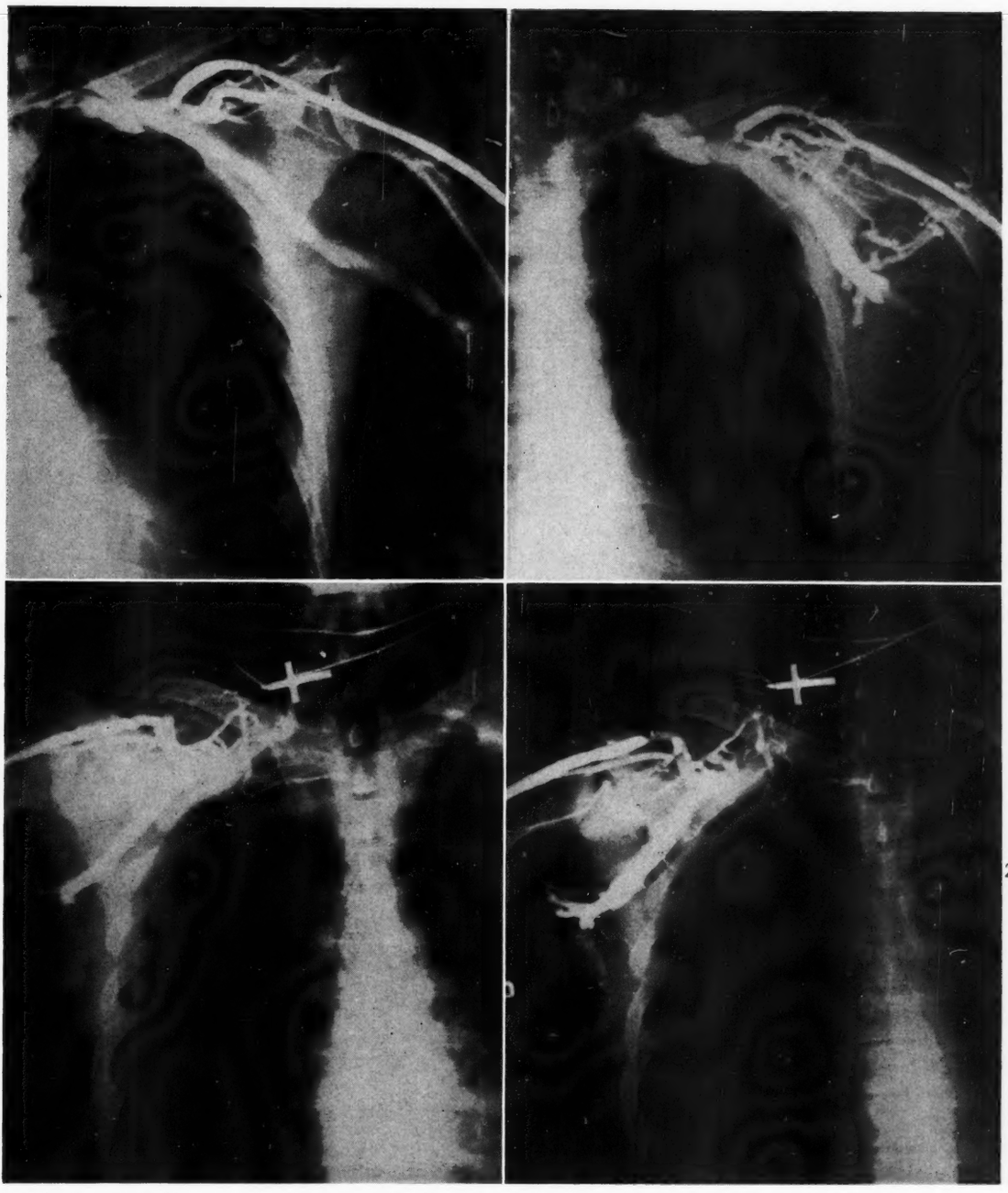
pressure rises within approximately one second of the beginning of the maneuver and falls within two seconds after its cessation.[4] Pressures taken in the esophagus, stomach, rectum, spinal canal and veins show an increase during the experiment.[3] Respiratory arrest and the increased pressure in the thoracic and abdominal cavity cause stasis in the veins of the greater circulation outside of the body cavity. The heart would become devoid of blood if it were not for the blood depots in the abdomen, liver and splanchnic vessels.[3]

Venography has provided an adequate direct method for the demonstration of the patency of a venous channel. As a corollary, it has been useful in assisting in the diagnosis of occlusion of a vein. The roentgen criteria for the diagnosis of venous occlusion are: (1) an abrupt interruption of the radiopaque substance coursing through the particular vessel, (2) distention of the vein distal to the point of interruption, (3) prominence of valves in the vessel distal to the block and (4) the appearance of the radiopaque substance in collateral vessels not normally visualized in the vicinity of occlusion.

It was observed in a number of films that a physiologic block was induced during the Valsalva experiment by the increased intravenous pressure. In several instances this was so marked that the venograms fullfilled the criteria already noted for the diagnosis of occlusion of a vein. Since the technic of venography requires venopuncture, the pain produced therefrom or the excitement of the procedure, or both, may cause a patient to hold his breath and strain. This would inadvertently increase intrathoracic and, secondarily, intravenous pressure. It is thus possible that a roentgenogram taken under such circumstances may show a picture resembling occlusion of a vein when, in fact, no organic occlusion exists. Therefore, to obtain a venogram valid for the roentgen diagnosis of venous obstruction one must guard against the inadvertent performance of a Valsalva experiment by the patient. This admonition is particularly important during angiocardiography in which serial exposures must be obtained within approximately nine to sixteen seconds (arm to tongue circulation time, saccharin or decholin, nine to sixteen seconds). It is possible for a patient while straining and holding his breath to retard venous blood flow in the peripheral circulation and actually to arrest this flow, at the level of the first rib, outside of the thorax, for a period as long as the Valsalva experiment is maintained, which can easily be sixteen seconds. Thus during serial angiocardiography all films may show no radiopaque material, or the last film to be exposed may show the material just entering the heart. The examiner must therefore pay special attention to the respirations of the patient to prevent straining and breath-holding. (Figs. 1 and 2.)

During the Valsalva experiment thirty-three of the fifty-two patients showed an arrest of venous flow at the margin of the first rib, where the axillary vein empties into the subclavian vein. In the control group only six showed an apparent arrest at this point. This, obviously, is a significant difference. In the remaining forty-six of the control group not only was the injected vein in the arm visualized but also the axillary, subclavian and innominate vein and the superior vena cava. That the six in the control group showed an apparent arrest at the margin of the first rib was probably due to premature radiographic exposure before the contrast media had an opportunity to reach the subclavian vein. In the experimental group the roentgenograms of the nineteen cases which showed no arrest at the margin of the first rib were probably the result either of too rapid injection of the radiopaque substance by the operator, or a slowly induced Valsalva experiment which permitted the radiopaque substance to reach the subclavian or innominate vein before the increased intrathoracic pressure interrupted the flow of blood.

Arrest of venous blood flow at the margin of the first rib during the Valsalva experiment is of more than passing interest. Axillary and subclavian vein thrombosis have most often been shown to occur secondary to (1) neoplasm, (2) operative scar, (3) heart failure and (4) trauma or effort.[10] The mechanism of thrombosis is quite apparent in association with local neoplasm and operative scar. The causes of the thrombosis in heart failure are not so clear but have been well reviewed by Loring.[36] Thrombosis of the axillary and subclavian vein following effort has been the object of much study, particularly as to the factors involved. Almost all observers are agreed that there is an anatomic background for the great frequency with which, following effort, thrombosis of a vein of the upper extremity is almost always likely to involve the axillary or the subclavian vein. Since little pathologic material has been avail-



1A 1B

2A 2B

FIG. 1. A, control film: note cephalic vein, basilic vein, axillary vein, subclavian vein. B, Valsalva experiment: injection made through same needle in same vein. Note arrest of flow and marked filling of anastomotic channels around shoulder joint; physiologic block.

FIG. 2. A, control film: note cephalic vein, axillary vein, right innominate vein, superior vena cava. B, Valsalva experiment: injection made through same needle in same vein. Note arrest of flow at first rib and increased filling of collateral veins around shoulder joint, including lateral thoracic veins; physiologic block.

able (one case)[11] for the study of thrombosis of the axillary or subclavian vein following effort, most explanations for what actually occurs locally have been based on hypotheses fortified by (1) clinical observations, (2) anatomic dissections on the cadaver, (3) venography and (4) operation during which part of the involved vein could be observed, albeit not adequately.

There are many who believe that effort thrombosis of the axillary or subclavian vein is due to injury to the intima.[12–14] While this concept is credible, it has never been demonstrated. Others have accented the role of venous stasis during forced expiration (Valsalva experiment) which characterizes effort.[13–15] Some invoked a concomitant injury of the intima.[13–15]

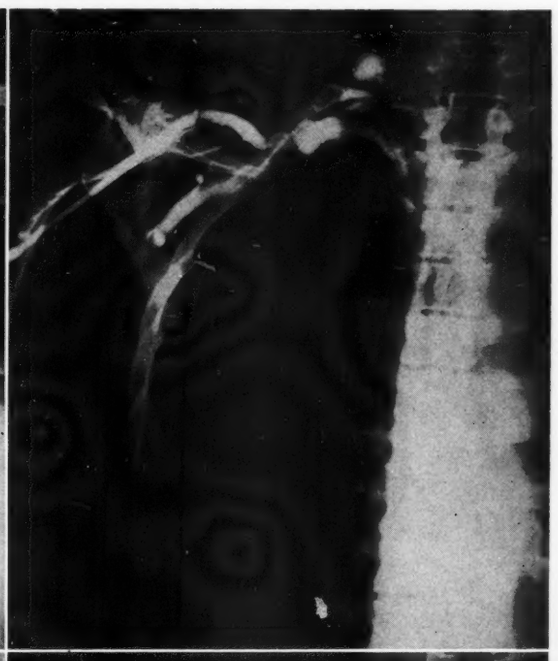
Exactly how and at what point effort traumatizes the axillary or subclavian vein has been the subject of much debate. Lahaussois[15] suggested that effort causes an augmented tension of the aponeurosis and vessels. In 1924 Lowenstein,[14] after dissecting nine bodies, pointed out the important relationship of the subclavius muscle and the costocoracoid membrane to the axillary vein. He believed that marked abduction of the arm or extension of the arm produced pressure by the costocoracoid membrane on the distended axillary vein. Lannon and Rudolph in 1947,[16] as a result of sixteen dissections, came to a similar conclusion regarding the importance of the subclavius muscle and the costocoracoid ligament in causing compression of the axillary vein. Sampson et al. in 1940,[17] and Sampson again in 1943,[18] presented the hypothesis that body build and posture associated with broad, horizontally curving first ribs and posteriorly directed clavicles, by narrowing the space between the clavicle and the first rib, predispose to effort thrombosis as well as to chronic compression of the subclavian vein. Intermittent obstruction of the subclavian vein due to venospasm has been observed by McLaughlin and Popma.[19] Cottalorda,[20] Lohr[21] and Hammann[22] believed that primary or secondary spasm of the vein was induced by trauma and that thrombosis was not necessary for venous obstruction. In 1946 MacCarthy[23] likewise observed the syndrome of axillary subclavian block due to venospasm. Veal and McFetridge,[24] as a result of venographic studies, concluded that obstruction of the axillary vein occurs below the head of the humerus and against the subscapularis muscle and not at the first rib. This has not been confirmed.

Since venous thrombosis following effort involving the upper extremity almost always involves the axillary or subclavian vein, it follows reasonably that the special predilection of involvement at this site is due primarily to anatomic features. According to most investigators these features are: (1) narrowing of the space between the first rib and the clavicle as a result of anatomic variations, (2) compression of the axillary subclavian vein (during effort) against the first rib by the costoclavicular ligament and its continuation, the costocoracoid ligament and (3) compression of the axillary subclavian vein against the first rib by the subclavius muscle and its tendon which becomes intimately associated with the costocoracoid and costoclavicular ligaments. Besides these factors many have emphasized the importance of the physiologic factor of increased venous pressure which results in venous distention and slowing of blood flow in the axillary and subclavian vein during effort.

Our studies showed that during the Valsalva maneuver, the flow of blood through the axillary subclavian vein is frequently arrested at the margin of the first rib. While the normal venous pressure in the antecubital fossa is 40 to 80 mm. of water, it may rise to 500 to 700 mm. of water during the Valsalva experiment. If such an enormous increase of pressure may occur in a vein in the antecubital fossa, it is safe to assume that the venous pressure in the axillary or subclavian vein will, in like manner, increase almost tenfold. The effect of this increased pressure is to distend the axillary subclavian vein and make it more rigid. This distended and more rigid vein, which lies in the interval between the clavicle and the first rib, offers increased resistance to the forces which act during effort upon the outside of the vein. It is reasonable to assume that injury to the vein wall may occur during effort at the margin of the first rib. The vein wall is the focal point upon which the increased venous pressure from within and the muscular, tendon and bone pressures from without will act.

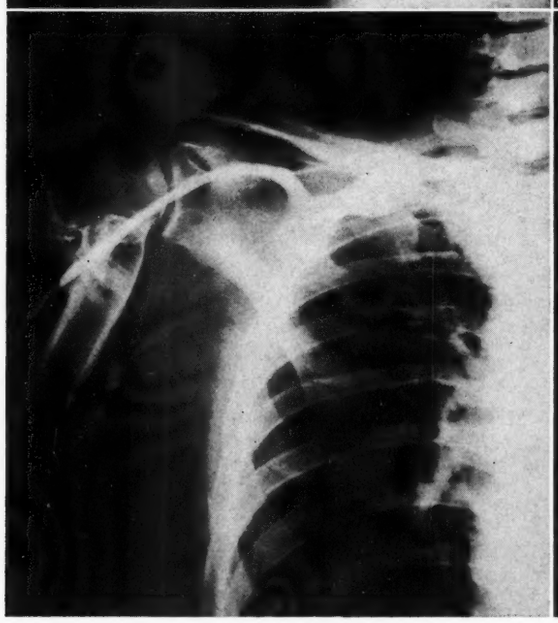
Just what the nature of the injury to the vein is has not been determined. Older investigators[12,13,14] assumed injury and perhaps ulceration of the venous endothelium. More recent investigators suggested that injury of a microscopic nature may predispose to thrombosis. Raeburn[25] has suggested that biochemical changes allow the permeation of collagenous

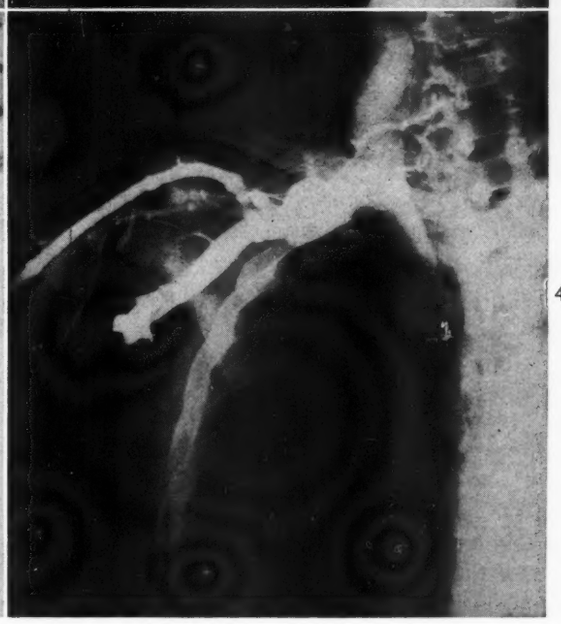
3A



3B

4A

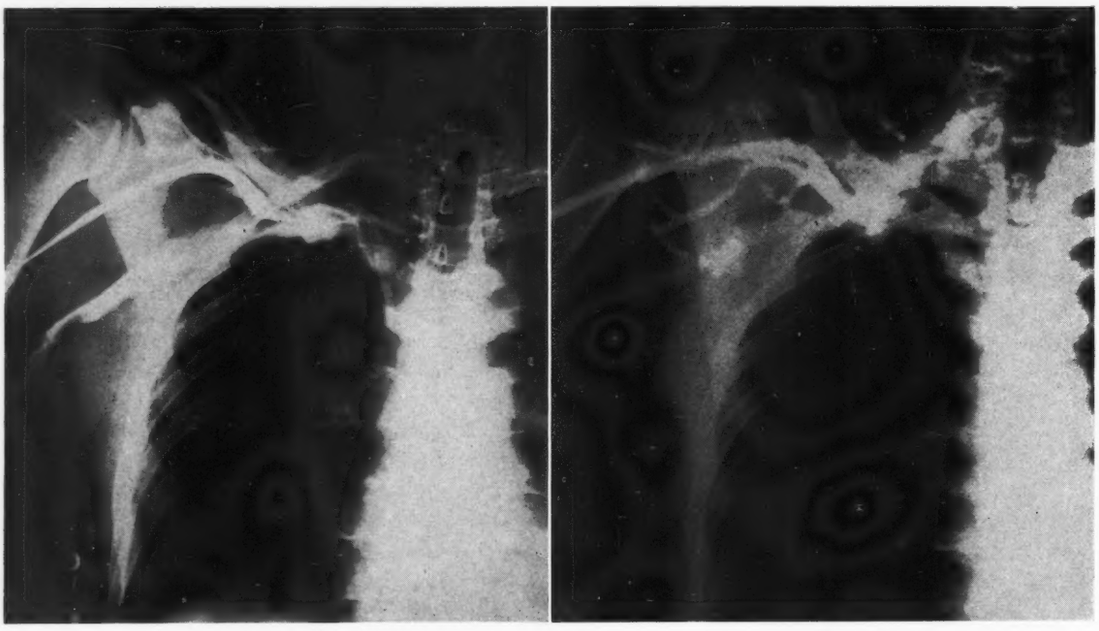




4B

FIG. 3. A, control film: note cephalic vein, basilic vein, axillary vein, subclavian vein, right innominate vein and superior vena cava. B, Valsalva experiment: injection made through same needle in same vein. Radiopaque material had entered thoracic inlet before intrathoracic pressure reached maximum. Note retrograde flow into vessels of the neck, i.e., lower portion of internal jugular vein and inferior thyroid vein.

FIG. 4. A, control film: note cephalic vein, basilic vein, axillary vein, subclavian vein, right innominate vein. B, Valsalva experiment: injection made through same needle in same vein. Radiopaque material had entered thoracic inlet before intrathoracic pressure reached maximum. Note retrograde flow into vessels of the neck, i.e., internal jugular vein and deep cervical veins.



5A 5B

FIG. 5. A, control film: note cephalic vein, basilic vein, axillary vein, subclavian vein. B, Valsalva experiment: injection made through same needle in same vein. Radiopaque material had reached innominate vein before intrathoracic pressure reached maximum. Note retrograde flow into vertebral vein and its tributaries from the vertebral bodies.

cement substance from between the endothelial cells. This substance is sticky and predisposes to platelet agglutination and thrombus formation. He was able to express such a substance from the venous endothelium. It may be that the physical forces outlined above are capable of expressing such a substance. The work of O'Neill[26] suggests that injury to the venous vasa venarum, associated with slowing of the circulation, may result in endothelial damage and predispose to thrombosis. At any rate, the exact nature of the local vein pathology which results in actual thrombus formation is not known.

In the course of our studies it was observed that when radiopaque material passed the first rib and reached the subclavian or innominate vein before the intravenous pressure increased enough to arrest venous flow at the margin of the first rib, the radiopaque material was forced to move in a retrograde fashion into channels it ordinarily would not have taken. Thus in some of our experiments we noted retrograde flow into the external jugular vein, the internal jugular vein, the thyroid vein, the vertebral vein, the thyrocervical trunk, etc. The retrograde flow of venous blood into the vertebral system of veins during the Valsalva experiment confirmed in living man the inferences of Batson[27] derived from his anatomic and animal studies. (Figs. 3, 4 and 5.)

The clinical anatomy of the spinal veins has long been known. Harris[28] reviewed the older literature and showed that the spinal veins were well known over 200 years ago and that the vertebral vein system was accurately described in 1823. He also pointed out that the vertebral system of veins was long ago referred to as vertebral sinuses. Hilton[28a] in 1855 noted the absence of valves in these veins and considered this of value because it enabled blood to pass in either direction. Cruveilhier[28b] in 1839 spoke of the spine as providing an uninterrupted communication between the veins of all parts of the trunk, so that either of the two vena cava could be obliterated without interruption of the venous circulation. McDowel[28c] in 1836 likewise called attention to the veins of the spinal column which served to connect the branches of the superior vena cava with those of the inferior vena cava.

Batson demonstrated the communications of the peripheral systemic veins with those of the vertebral system by means of the injection of radiopaque material into veins of a cadaver. He injected the dorsal vein of the penis and

showed that the radiopaque material did not of necessity pass into the caval system but could progress up the spinal and vertebral veins and reach vertebrae, ribs, base of the skull and the cranial cavity. The material could also be traced to the sacrum and pelvis. In another experiment he injected a small vein in the breast of a cadaver and traced the material to the clavicles, head of the humerus, cervical vertebrae and cranial venous sinuses as well as to the azygos vein and the superior caval system.

Batson duplicated his anatomic experiment in the living animal (monkey) by compressing the inferior vena cava and injecting the dorsal vein of the penis with radiopaque material. He could follow the material in roentgenograms past the zone of compression by way of the vertebral system into the vessels of the lower thoracic spine and into the lower intercostal veins. He reasoned from this that it would be possible that during the Valsalva maneuver not only for blood to be prevented from entering the chest and abdominal cavities but even to be squeezed out of the intra-abdominal veins into the vertebral system. Batson developed the concept that these valveless vertebral veins were constantly and physiologically the site of frequent reversals of venous blood flow.

To the studies of Batson we have added our own direct observation of reversal of blood flow in normal man during the Valsalva maneuver. We have shown that a radiopaque substance injected into the cephalic or basilic vein in the antecubital fossa could reach the veins of the neck, the jugular vein, thyroid vein, vertebral vein, etc. Since the material passes into the vertebral vein by way of the innominate vein, our experiments complement Batson's cadaver experiments in which a mammary vein, likewise a tributory of the innominate vein, carried radiopaque material to the vertebral vein.

Batson's studies[27,29,30] were important because they clearly crystallized concepts regarding the function of the vertebral veins and their role in the spread of metastases. These concepts made the appearance of metastatic abscess and tumor in unusual locations more comprehensible. The classical channels through which metastases spread, i.e., via the caval systems, pulmonary systems, lymphatic system or direct extension, could not account for these loci without interposing assumptions which often were not credible.

The vertebral system of veins is said to include the epidural veins, perivertebral veins, veins of the thoraco-abdominal wall, veins of the head and neck and the veins of the blood vessels of the extremities. The anatomy of the vertebral veins is such that there are rich anastomoses around the spinal column and within the bones of the column and of the veins of the spinal cord. These vessels communicate with segmental veins in the thoraco-abdominal wall. The longitudinal vertebral veins duplicate their size and pattern from segment to segment and connect with the veins of the body cavity at each segmental level. The vertebral veins provide a direct pathway from the pelvic veins to the cranial venous sinuses. These veins are valveless and carry blood under low pressures. Blood flow in these veins is constantly subject to arrests and reversals. This system of veins parallels and provides by-passes for the portal, pulmonary and caval systems. During the acts of sneezing, straining, coughing or lifting with the upper extremity (Valsalva experiment) blood is not only prevented from entering the thoraco-abdominal cavity but is actually squeezed out of the cavity. During these acts tumors or abscesses which have any venous communication with the vertebral system of veins may distribute metastases anywhere along the vertebral system without involving the portal, pulmonary or caval systems.

Norgore[31] repeated and confirmed Batson's experiments. Coman and deLong[32] demonstrated the role of the vertebral veins by controlled animal experiments in which viable embolic tumor cells were injected into the femoral vein with and without compression of the inferior vena cava. They demonstrated that with compression of the inferior vena cava (thus simulating the effect of the Valsalva experiment) these tumor cells passed directly to the vertebrae by way of the vertebral veins while by-passing the lungs. The tumor cells remained in the vertebrae and continued their growth. Clinically, such observations as metastatic brain abscess following suppurative lung disease,[33] lumbar vertebral metastases as the first evidence of breast carcinoma,[34] metastases to the mandible from breast carcinoma,[35] and metastases to the vertebrae, ribs, pelvis, skull from carcinoma of the prostate[27] can be most readily explained by pathways which depend anatomically upon the vertebral veins and physiologically upon the characteristic reversal of blood flow which

occurs in these veins during periods of increased intrathoracic and intrabdominal pressure (Valsalva experiment) accompanying many normal physiologic acts of man.

SUMMARY AND CONCLUSIONS

The venous pathways of the arm, neck and chest of fifty-two young men with normal cardiovascular systems were studied. In each subject a radiopaque substance was injected into a vein in the antecubital fossa and a control venogram was obtained at the end of quiet inspiration. Through the same needle in the same vein another injection was made while the patient was performing a Valsalva experiment (forced expiration with a closed glottis) and another venogram obtained. Comparison of the experimental films with the control films showed that during the Valsalva maneuver (1) the radiopaque substance was frequently arrested at the level of the first rib; (2) venograms were obtained which fulfilled the criteria for the diagnosis of venous occlusion of the axillary or subclavian vein; (3) there was a retrograde flow of radiopaque substance around the shoulder joint and into the veins of the neck, i.e., cervical, vertebral, inferior thyroid, internal and external jugular veins.

In the course of venography for the purpose of diagnosis of venous occlusion precautions should be taken to avoid an unintentional Valsalva maneuver on the part of the patient because a venogram could be obtained in a normal venous system, under conditions of the Valsalva experiment, which would exhibit all the features of venous occlusion.

The importance of arrest of blood flow and increased venous pressure at the level of the first rib during the Valsalva maneuver was discussed as one of the factors which contribute to the occurrence of axillary or subclavian vein thrombosis during effort.

The role of retrograde flow into vessels of the neck is discussed in connection with the significance of this phenomenon in explaining unusual sites of infections or neoplastic metastases.

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Decreased Hallucal Circulation, an Early Manifestation of Vascular Disease in Diabetes Mellitus*

MILTON MENDLOWITZ, M.D., EDWARD B. GROSSMAN, M.D. *and* SAMUEL ALPERT, M.D.
New York, New York

In 1930 Starr[1] found decreased circulation in the feet of diabetic patients without demonstrable obstruction of large arteries. He could not determine whether this was caused by vasospasm or structural occlusion of small blood vessels. Megibow et al.[2] noted in 1949 that twelve of forty-eight young patients with uncomplicated diabetes mellitus had decreased hallucal circulation as measured plethysmographically. In 1952 Handelsman et al.[3] demonstrated a less than normal increase in the skin temperature of the toes after the injection of 2-benzyl imidazoline hydrochloride (priscoline®) in a small number of patients with uncomplicated diabetes mellitus. Our study began as an attempt to corroborate these findings by another technic.

In the present study, circulation in the great toe was measured calorimetrically in a group of thirty-eight diabetic patients and thirty control subjects by a method previously described by one of us.[4] In both the diabetic and the control groups all subjects were under the age of fifty years and the age distribution in the two groups was similar. Four diabetic patients were excluded from the original group because of the presence of retinal vascular changes and four others because of x-ray demonstration of calcification of the arteries of the lower extremities. One patient in each of these two categories was found to have decreased hallucal circulation in addition to retinitis or vascular calcification. The only other subjects excluded from the diabetic group were those who were over the arbitrarily set age limit, those with overt neuropathy or cardiovascular renal disease, and patients whose diabetes was known to have been of more than ten years' duration. This left a group of relatively young diabetic patients with normal ocular fundi, normal oscillometric readings, no visible arterial calcification on x-ray examination of the lower extremities and no evidence of cardiovascular or renal disease as revealed by clinical examinations, urine analyses, routine renal function tests, electrocardiograms and chest roentgenograms. Liver function tests, including bromsulfalein, cephalin flocculation, thymol turbidity, serum bilirubin and proteins, were also within normal limits in these patients except for occasional increases in cephalin flocculation and thymol turbidity. These changes were usually borderline however, and were seen not infrequently in many otherwise normal patients. Standard methods were used for the laboratory tests. Blood cholesterol (Bloor[5]) and phospholipid (Youngburg[6]) determinations were also made in an attempt to correlate vascular disease with chemical changes.

The control group consisted of people without diabetes or vascular disease. Some had duodenal ulcers, some were psychoneurotic or had mild skin disease and the remainder were normal men. No women were included in either group.

Hallucal circulation was measured after inhibition of sympathetic nerve discharge by approximately one hour of indirect heating, supplemented by the intravenous injection of tetraethylammonium chloride in dosage of 5 mg. per kg. of body weight. At least two tests were carried out in each individual and when there

* From the Veterans Administration Regional Office, New York, N. Y., and Department of Medicine, The Mount Sinai Hospital, New York. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration. Aided by a grant from the National Heart Institute, National Institutes of Health, the U. S. Public Health Service, Bethesda, Md.

TABLE I
CONTROL SERIES A

Case No.	Age	Blood Flow (cc./sq. cm./min.)	Date of Test
1	39	0.23	3-4-52
		0.22	3-12-52
2	34	0.25	3-11-52
		0.28	3-19-52
3	31	0.17	5-12-50
		0.10	2-19-52
		0.16	3-10-52
4	32	0.18	3-7-52
		0.21	3-18-52
5	34	0.17	3-6-52
		0.22	3-25-52
6	32	0.17	8-11-49
		0.13	2-8-52
		0.20	4-4-52
7	41	0.23	6-6-49
		0.19	2-7-52
8	30	0.29	10-19-49
		0.23	12-20-51
9	44	0.24	10-21-49
		0.11	10-9-51
		0.21	12-7-51
10	34	0.20	8-18-49
		0.25	10-25-51
11	41	0.26	11-2-49
		0.22	10-23-51
12	32	0.24	6-27-49
		0.22	10-18-51
13	30	0.21	3-14-52
		0.21	3-17-52
14	38	0.27	11-3-49
		0.23	10-17-51
15	45	0.19	12-2-49
		0.24	10-16-51
16	29	0.15	6-17-49
		0.23	6-17-49
17	22	0.21	1-12-50
		0.22	1-17-50
		0.28	4-20-50
18	46	0.17	3-6-52
		0.12	3-18-52
		0.18	4-4-52
19	22	0.19	1-18-52
		0.18	3-7-52
20	44	0.21	2-21-52
		0.15	3-5-52
21	28	0.12	3-4-52
		0.15	3-5-52
22	41	0.15	2-7-52
		0.27	2-8-52
23	45	0.16	1-29-52
		0.16	1-30-52
24	26	0.14	1-5-50
		0.20	1-26-52
25	46	0.17	1-22-52
		0.21	1-23-52
26	23	0.17	1-11-52
		0.17	1-15-52
27	17	0.25	10-7-49
		0.27	1-10-52
28	25	0.25	1-29-52
		0.27	4-1-52
29	45	0.32	12-31-51
		0.28	3-24-52
30	31	0.20	1-24-52
		0.24	3-26-52

was significant discrepancy between the two readings a third test was done. These tests were usually accomplished in the mornings. It was found that, if the patients who had been using protamine zinc insulin were fasting, heat and tetraethylammonium chloride could potentiate the effect of residual insulin in occasional cases and bring the blood sugar down to hypoglycemic levels with resultant vomiting and shock. Blood sugar determinations revealed that if the diabetic patients had their insulin and breakfast as usual prior to the test, heat and tetraethylammonium chloride did not produce hypoglycemia. All the studies reported here, therefore, were done in this way. The degree of control was evaluated on the basis of results of daily urine analyses by the patients, checked in the laboratory at least once and more often twice a month, and less frequent fasting blood sugar

TABLE II
CONTROL SERIES B

Case No.	Cholesterol (mg./100 cc.)	Phospholipid (mg. P/100 cc.)	Cholesterol-phospholipid Ratio $\left(\frac{C}{25\ P}\right)$
1	210	8.8	0.95
2	230	9.1	1.01
3	157	10.2	0.68
4	184	9.0	0.82
5	186	8.7	0.86
6	178	9.6	0.74
7	218	9.5	0.90
8	256	8.2	1.25
9	288	9.4	1.23
10	270	13.2	0.82
11	310	13.5	0.92
12	173	6.4	1.08
13	242	10.2	0.95
14	230	13.9	0.66
15	200	13.9	0.58
16	294	9.3	1.26
17	310	14.1	0.80
18	242	8.8	1.10
19	302	10.3	1.17
20	236	9.6	0.98
21	288	7.2	1.60
22	310	10.6	1.17
23	194	7.3	1.06
24	224	8.6	1.04
25	204	9.3	0.87
26	188	10.5	0.70
27	242	13.2	0.73
28	348	12.8	1.09
29	270	11.8	0.88
30	320	16.8	0.76

TABLE III

DIABETES MELLITUS

Case No.	Age	Year of Onset	Insulin Dosage	Degree of Control	Cholesterol (mg./100 cc.)	Phospholipid (mg. P/100 cc.)	C./P. ratio C/(25 P)	Blood Flow (cc./sq. cm./min.)	Date of Test
1	42	1949	NPH 10	Good	254	8.9	1.14	0.16	1-13-50
								0.18	3-1-50
2	44	1945	NPH 44 R 4	Good	301	10.35	1.05	0.19	12-1-49
								0.13	12-21-50
								0.22	8-14-51
3	40	1945	NPH 48 R 5	Poor	260	11.2	0.93	0.14	12-1-50
								0.12	3-6-51
4	33	1945	PZI 70	Poor	227	7.6	1.20	0.15	1-6-50
								0.21	11-30-50
5	46	1944	NPH 60	Fair	157	7.0	0.90	0.24	11-2-50
								0.21	6-29-51
6	34	1943	NPH 50	Poor	222	10.3	0.80	0.10	12–5–49
								0.21	5-2-51
								0.17	8-22-51
7	30	1946	NPH 55 R 10	Poor	328	8.7	1.51	0.24	10-16-50
								0.12	3-19-51
								0.22	7-23-51
8	38	1945	PZI 36	Fair	310	9.0	1.38	0.24	11-7-50
								0.28	5-7-51
9	43	1945	NPH 45	Poor	358	15.2	0.94	0.12	8-21-51
								0.09	1-8-52
10	32	1945	PZI 68	Fair	194	8.2	0.95	0.15	12-20-50
								0.25	5-26-51
11	35	1946	NPH 68	Fair	283	11.6	0.97	0.03	1-16-50
								0.06	2-3-50
12	34	1946	O	Fair	265	10.0	1.06	0.17	1-18-50
								0.28	8-17-51
13	46	1944	NPH 42	Fair	194	9.2	0.84	0.25	12-25-49
								0.27	10-5-50
14	34	1945	NPH 50	Fair	...	.....	....	0.19	12-5-49
								0.15	10-23-50
15	27	1946	NPH 60	Poor	270	12.8	0.84	0.21	1-27-50
								0.19	9-18-51
16	34	1945	NPH 80	Poor	...	.....	....	0.21	10-16-50
								0.20	10-13-51
17	36	1943	PZI 18 R 24	Fair	184	7.42	0.99	0.13	11-14-50
								0.18	8-16-51
								0.12	2-15-52
18	41	1948	NPH 68	Poor	185	8.3	0.89	0.24	12-13-49
								0.32	10-25-50
19	25	1946	NPH 55	Poor	264	10.9	0.97	0.22	12-16-49
								0.21	7-13-51
20	28	1946	NPH 65	Poor	196	8.0	0.98	0.21	1-3-50
								0.20	11-8-50
21	31	1947	O	Good	...	.....	....	0.08	1-12-51
								0.20	7-31-51
22	30	1946	NPH 65	Poor	264	9.5	1.11	0.15	10-3-50
								0.17	2-4-52
23	40	1946	NPH 35	Good	260	12.9	0.80	0.05	12-13-50
								0.08	5-29-51
24	28	1948	PZI 17 R 34	Fair	231	9.35	0.99	0.25	12-29-49
								0.22	4-11-51
25	35	1945	PZI 48	Fair	248	10.0	0.99	0.07	12-29-49
								0.07	3-6-51

TABLE III—(*Continued*)

Case No.	Age	Year of Onset	Insulin Dosage	Degree of Control	Cholesterol (mg./100 cc.)	Phospholipid (mg. P/100 cc.)	C./P. ratio $\frac{C}{(25\ P)}$	Blood Flow (cc./sq. cm./min.)	Date of Test
26	41	1944	PZI 70	Fair	228	8.9	1.02	0.25	11-2-50
								0.19	6-22-51
27	42	1945	NPH 68	Poor	298	12.0	0.99	0.16	11-25-49
								0.14	10-5-50
28	25	1946	PZI 30 R 45	Good	189	9.3	0.81	0.09	2-2-51
								0.13	3-9-51
29	43	1945	NPH 15	Good	260	10.4	1.00	0.06	1-20-50
								0.11	8-31-51
30	35	1946	NPH 68	Fair	242	8.8	1.10	0.09	5-14-51
								0.19	9-4-51
								0.13	2-18-52
31	30	1946	NPH 50	Poor	234	10.6	0.90	0.19	1-17-50
								0.24	10-4-50
32	54	1943	O	Good	234	9.3	1.01	0.15	1-12-50
								0.17	5-29-51
33	44	1945	NPH 70	Poor	...	12.0	....	0.13	10-5-50
								0.10	3-14-51
34	24	1947	PZI 12 R 24	Fair	216	9.0	0.96	0.09	12-5-50
								0.05	7-18-51
35	31	1944	PZI 40 R 56	Poor	314	11.1	1.13	0.24	10-11-50
								0.13	3-9-51
								0.14	2-12-52
36	30	1945	NPH 68 R 10	Poor	352	12.5	1.11	0.18	1-16-50
								0.21	12-6-50
37	36	1946	NPH 100	Poor	230	8.2	1.12	0.25	12-22-49
								0.23	11-17-50
38	29	1944	NPH 70	Fair	240	9.5	1.01	0.08	1-13-50
								0.19	10-24-50
								0.24	10-26-51

determinations (Folin-Wu method[7]). On this basis, the degree of control was labeled either poor, fair or good. None of these patients was under the type of control classified by Wilson et al.[8] as excellent.

RESULTS

Nine of the thirty-eight patients in the diabetic group had blood flow readings which on repeated testing were persistently below the lower limit of normal (0.15 cc./sq. cm./min). (Tables I, II, III and IV and Fig. 1.) Statistical analysis of the lowest, highest and average (means of two or three tests in each patient) readings in each group revealed significant differences between the diabetic and the non-diabetic group. Discrepancies between the two or three tests in some cases in both groups indicated that inhibition of sympathetic nerve discharge by the procedure used was incomplete in occasional tests. This occurred to approximately the same extent in each group. Although blood cholesterol was higher, phospholipid lower and cholesterol-phospholipid ratio higher in the diabetic than in the control group, the statistical significance of these differences was slight. The probabilities that the differences were due to chance were, greater than 0.5, 0.3 and 0.2 respectively. Nor could any significant correlation be established between the decreased circulation and the blood chemical findings, duration, severity or degree of control of the disease in the diabetic group.

COMMENTS

These studies indicate that decreased circulation in the great toe may be the earliest manifestation of vascular disease in diabetes since a persistent decrease on repeated testing occurred in approximately one-fourth of these diabetic patients in whom no other evidence of vascular disease was found. In an occasional case, how-

TABLE IV
STATISTICAL ANALYSIS

Group	No. of Cases	Determination	Range	Mean	Standard Deviation	Standard Error of the Mean	Difference between the Means	Standard Error of the Difference between the Means	Probability That Difference Is Due to Chance
Control Series A	30	(1) Lowest blood flow in each patient—cc./sq. cm./min.	0.10–0.28	0.185	0.046	0.0083	0.045	0.0112	0.00006
		(2) Highest blood flow in each patient—cc./sq. cm./min.	0.15–0.32	0.230	0.041	0.0075			
		(3) Average of all blood flows in each patient—cc./sq. cm./min.	0.13–0.30	0.208	0.040	0.0073			
Diabetes	38	(4) Lowest blood flow in each patient—cc./sq. cm./min.	0.03–0.25	0.146	0.058	0.0095	0.049	0.0139	0.0005
		(5) Highest blood flow in each patient—cc./sq. cm./min.	0.06–0.32	0.195	0.062	0.0075			
		(6) Average of all blood flows in each patient—cc./sq. cm./min.	0.05–0.28	0.170	0.058	0.0093			
						(1) & (4)	0.039	0.0126	0.002
						(2) & (5)	0.035	0.0126	0.005
						(3) & (6)	0.038	0.0118	0.002

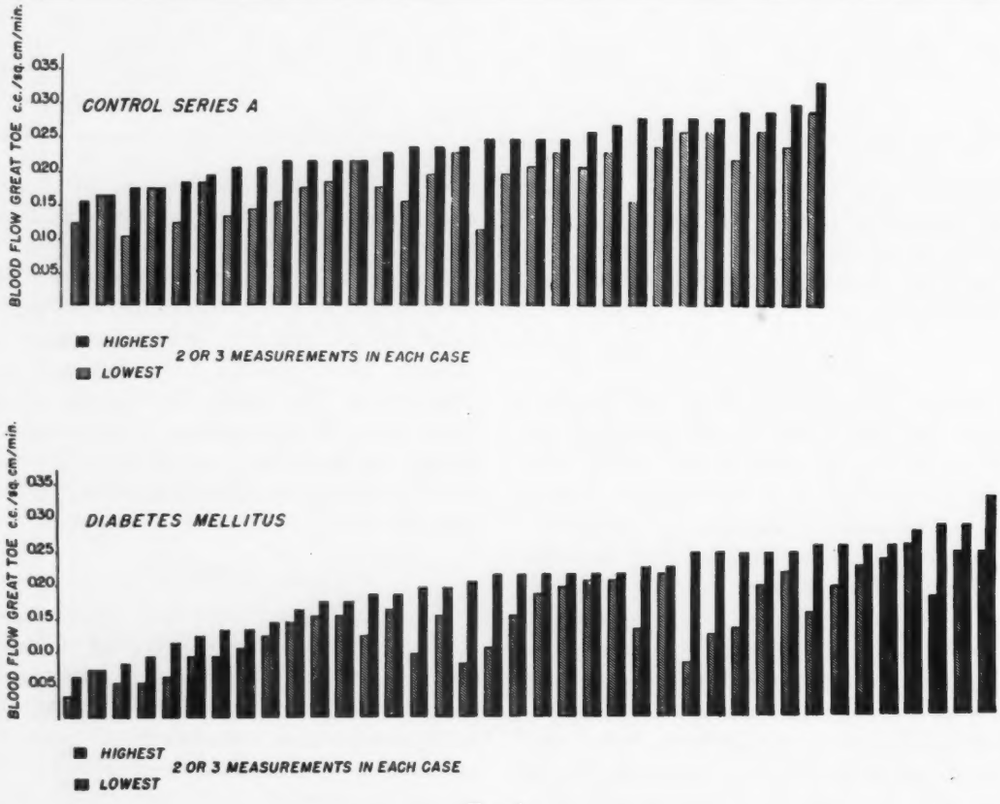

FIG. 1.

ever, retinitis or calcification of the arteries of the lower extremities may appear before decreased hallucal circulation is demonstrable.

It may be argued that the persistently low blood flow in patients with diabetes is caused by residual neurogenic vasomotor tone. The observation, however, that such vasospasm, as manifested by significantly different blood flow levels upon repeated testing, was found to be about as uncommon in the non-diabetic as in the diabetic group favors the view that changes in the diabetic patients represent organic vascular disease. On the basis of the data obtained in the control group, the probability that blood flow in two or more tests performed on any given subject will be persistently decreased because of residual neurogenic vasomotor tone is extremely small.

It has been suggested that the degree of control of carbohydrate metabolism may either directly or indirectly influence the development of vascular disease. This is deduced from the absence of vascular lesions in the very small percentage of patients classified by Wilson et al.[8] as under excellent control. Since none of our patients was in this category, this study throws no light on the point raised except to re-emphasize the thesis[9] that in the ordinary diabetic patient the degree of control cannot be correlated with the early appearance of vascular disease.

SUMMARY AND CONCLUSIONS

1. In a study of thirty-eight relatively young diabetic patients without overt evidence of vascular disease, persistently decreased hallucal circulation as measured calorimetrically was the earliest demonstrable manifestation of vascular impairment in nine of the cases.

2. Statistical evaluation of results obtained in this diabetic group and in a non-diabetic control group of thirty subjects revealed a significant decrease in hallucal blood flow in the diabetic patients.

3. No significant correlation could be established between cholesterol, phospholipid or cholesterol-phospholipid ratio and the depressed circulation in the great toe; nor could any correlation be found between the duration, severity or degree of control of the diabetes and the extent of the decrease in circulation.

4. The significance of these findings is discussed.

Acknowledgment: We are grateful to Miss G. Salzberg, Mr. H. Rothman, G. Wiener and P. Ciri for technical assistance and to Miss A. A. Zanetti, R.N., M. Ellingwood, R.N. and E. M. Elder, R.N., for invaluable help with our records.

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The Mechanism of Accelerated Peripheral Vascular Sclerosis in Diabetes Mellitus*

RAYMOND S. MEGIBOW, M.D., SAMUEL J. MEGIBOW, M.D., HERBERT POLLACK, M.D., JOHN J. BOOKMAN, M.D. *and* KERMIT OSSERMAN, M.D.

New York, New York

OCCLUSIVE peripheral vascular disease in the diabetic patient is generally considered to be identical histologically with peripheral arteriosclerosis in the non-diabetic subject.[1–3] The primary lesion in both is described as an intimal and subintimal atheromatosis of the larger arteries of the lower extremities. The recognized association of the clinical syndrome of diabetes mellitus with the development of premature and extensive arteriosclerosis is the usual explanation offered for any differences which may be found in the vascular patterns among comparable diabetic and non-diabetic groups.

The development of specific measures for the treatment and prevention of these vascular disorders awaits elucidation of their pathogenesis. At present one factor which limits the possible effectiveness of available therapeutic procedures is the relative insensitivity of diagnostic technics which are employed routinely for the study of the peripheral circulation. The recognition of clinical vascular disease by these methods is synonymous with advanced anatomic change. A diagnostic procedure capable of disclosing peripheral vascular alterations at their inception would be distinctly advantageous. It would offer an approach for the correlation of alterations in peripheral hemodynamics with the pathogenesis of the vascular derangement and thus obviate the otherwise confusing effect of secondary influences caused by well established disease. Furthermore, such a technic would afford a better means for evaluating the benefits of any therapeutic regimen which might be proposed.

One of us (R. S. M.) has employed a specially designed ink-recording photoelectric microplethysmograph for the study of the digital circulation.[4] Because of its reproductibility and sensitivity this instrument was considered to be especially suitable for analyzing the peripheral circulation in diabetes mellitus. It was thought that the microplethysmographic method might be expected to disclose early and otherwise inapparent structural vascular alterations.

MATERIAL AND METHODS

Sixty-one diabetic patients, all under the age of forty-five, were selected originally for this study. The age limit was imposed because of the expected high incidence of clinical arteriosclerosis in older non-diabetic groups. Fourteen patients who exhibited peripheral abnormalities by the usual diagnostic methods, namely physical examination, roentgenography and oscillometry, were excluded from further investigation. Of the remaining forty-seven patients, twenty-seven were females. Included in the series were subjects whose glycosuria was minimal and those whose glycosuria was uncontrolled.

All patients had been observed periodically in the Diabetic Clinic for extended periods. At intervals they underwent careful physical examination. Special attention was directed to the cardiac and peripheral circulatory status, to the level of the blood pressure and to the ophthalmoscopic findings. The urine was analyzed for the presence of reducing substances and ketone bodies, any necessary insulin and dietary adjustments being made on the basis of the findings. Tests for albumin in the urine and for formed elements were performed periodically.

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In the case of those patients maintained on a prescribed carbohydrate, fat and protein intake, an attempt at evaluating their adherence to the dietary regimen was made during each interview. The cholesterol content of the blood was determined at intervals by the Schoenheimer and Sperry method.[5] An electrocardiogram, a teleoroentgenogram and an x-ray of the lower extremities were obtained in each subject. The oscillometric index was measured in all patients at the levels of the mid-thigh, mid-calf and ankle. In selected cases the vasoconstrictor gradient was determined by means of a Leeds-Northrup potentiometer.

The technic and necessary precautions for adequate microplethysmographic recording have been detailed elsewhere.[6] The procedures which were employed in the study were explained carefully to each subject. This lessened anxiety and served to minimize the effect of psychic stimulation. The volume of each great toe was measured by water displacement and the ambient temperature was checked at the beginning and end of each experiment. All plethysmographic tracings were obtained after a preliminary rest period of twenty minutes.

Control microplethysmograms were recorded from the halluxes of each patient. The patient was then given nitroglycerine sublingually in doses ranging from 0.3 mg. to 0.6 mg., depending upon weight and age. Thereafter continuous tracings were obtained until the effects of the drug had been dissipated. On a separate occasion some patients received tetraethylammonium chloride intravenously in doses sufficient to induce functional ganglionic blockade. This was determined plethysmographically by the effects on alpha wave and reflex vasoconstrictor activity. Since these alterations in volume require an intact sympathetic innervation, their disappearance following the administration of tetraethylammonium was considered indicative of autonomic paralysis. All records were calibrated frequently to insure adequate standards for measurement. The rate of blood flow was computed at frequent intervals during the control period and during the period following drug administration by the venous occlusion method. The microplethysmograms were analyzed on the basis of amplitude of the volume pulse wave, rate of blood flow, slope of the blood flow curve and contour of the volume pulse wave.

Variations in digital blood flow may be enormous. For example, investigations have disclosed that the blood flow in the great toe of the normal subject may vary from as little as 1 cc. per min. per 100 cc. volume to as much as 150 cc. per min. per 100 cc. volume during maximal constriction and full vasodilatation. We have found that not infrequently vascular patterns obtained from corresponding digits in otherwise normal individuals reveal striking differences. These may result from variations in reflex activity since they disappear after release of vasomotor tone. In the presence of occlusive vascular disease discrepancies in pulse volume and blood flow are not ordinarily eliminated by autonomic blockade or by sympathectomy. For these reasons and because of the recognized differences in rate of blood flow and in pulse volume which may be found among normal subjects, the interpretation of results has been based upon a comparison of the component deflections of the microplethysmograms in each subject (*vide supra*). In this way one toe serves as a control for the contralateral toe.

Previous experiences with nitroglycerine have demonstrated that the drug is ordinarily capable of differentiating vasospastic from organic peripheral vascular disease. However, its value as an absolute indicator of the functional status of the digital circulation is limited in the presence of intense vasospasm.[4] Nevertheless, for purposes of the present study it was believed that preliminary testing with nitroglycerine might serve as a useful screening procedure. Thus any patient who manifested an equal degree of vasodilatation bilaterally after drug administration was presumed to be free of occlusive peripheral vascular disease. On the other hand, those patients who revealed significant differences in plethysmographic patterns in each toe were retested subsequently with tetraethylammonium. In this latter group final analysis of the peripheral circulation was based on the tracings after ganglionic blockade.

RESULTS

It has been found that the characteristic pulse wave alterations and the increased pulse volume which normally follow the administration of nitroglycerine (Fig. 1) are absent or are minimal in the presence of organic vascular disease.[4] (Fig. 2.) However, for purposes of the present study the patient was considered to possess an intact peripheral circulation when the tracings from both toes were similar even when the

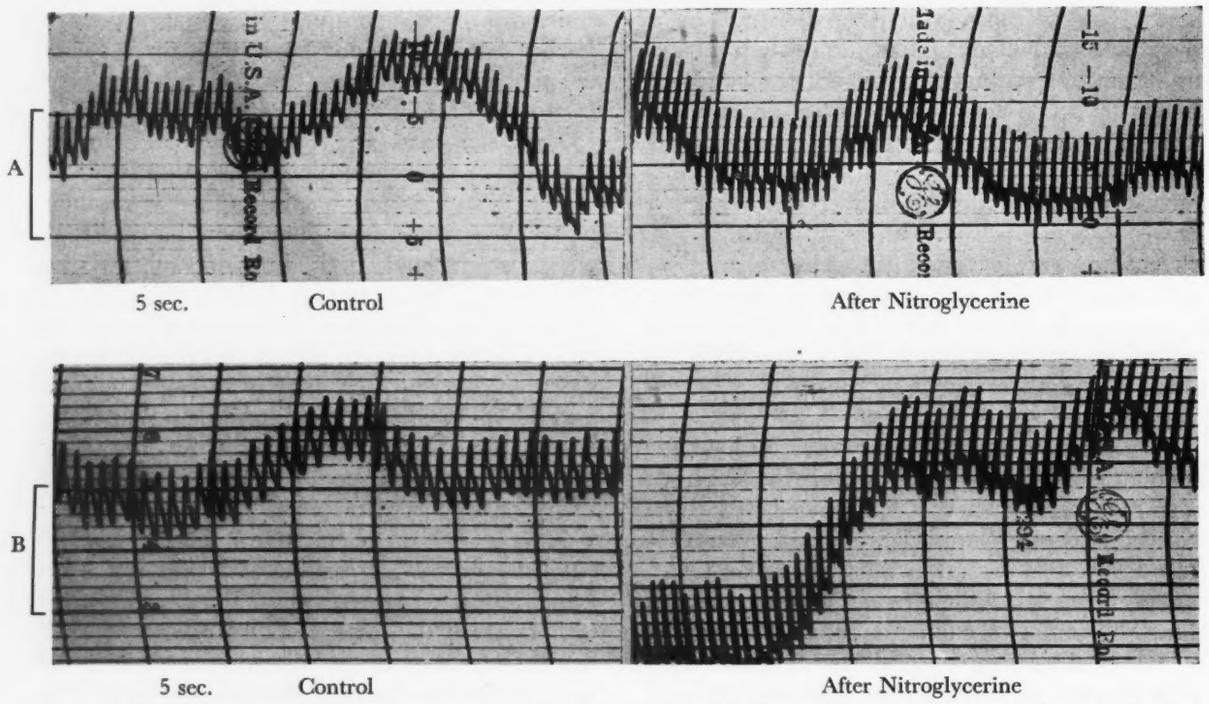


FIG. 1. Microplethysmograms from two normal subjects (A and B). Note the increased amplitude and dicrotism following nitroglycerine. (Calibration to left of tracings = 20 cu. mm.)

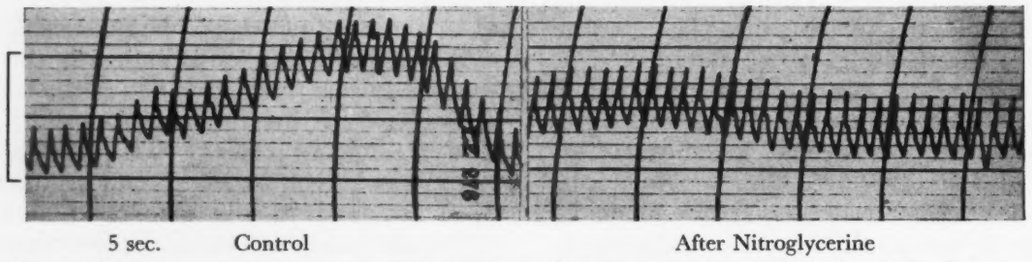


FIG. 2. Microplethysmograms from a patient with peripheral arteriosclerosis. Note the minimal changes in volume and contour following nitroglycerine. (Calibration to left of tracing = 20 cu. mm.)

over-all quantitative volume change was minimal. Despite these more rigid criteria, a microplethysmographic diagnosis of peripheral vascular disease was made in twenty-two of the forty-seven patients tested. (Table I.) This was based on the finding of a significant reduction in rate of blood flow and/or volume pulse amplitude in one hallux as compared with the contralateral digit. (Fig. 3.) These twenty-two patients were accordingly re-evaluated after the injection of tetraethylammonium. It was found that the variations in the digital circulation following nitroglycerine disappeared in seven patients. (Fig. 4.) This suggests that the initial differences in blood flow and pulse volume were the result of vasospasm. Fifteen patients remained who continued to exhibit significant differences in flow and amplitude in one as compared to the other great toe. (Fig. 5, Table II.) Major alterations in the contour of the pulse wave or in the slope of the blood flow curve were not observed. These findings are not unexpected since alterations in contour and in slope develop only in the presence of advanced occlusive peripheral disease.[7] Accepting the fact that reflex vasoconstrictor activity could be excluded on the basis of the plethysmographic criteria described previously, a reduction in blood flow and pulse volume implies the existence of an increase in fixed peripheral vascular resistance. Presumably

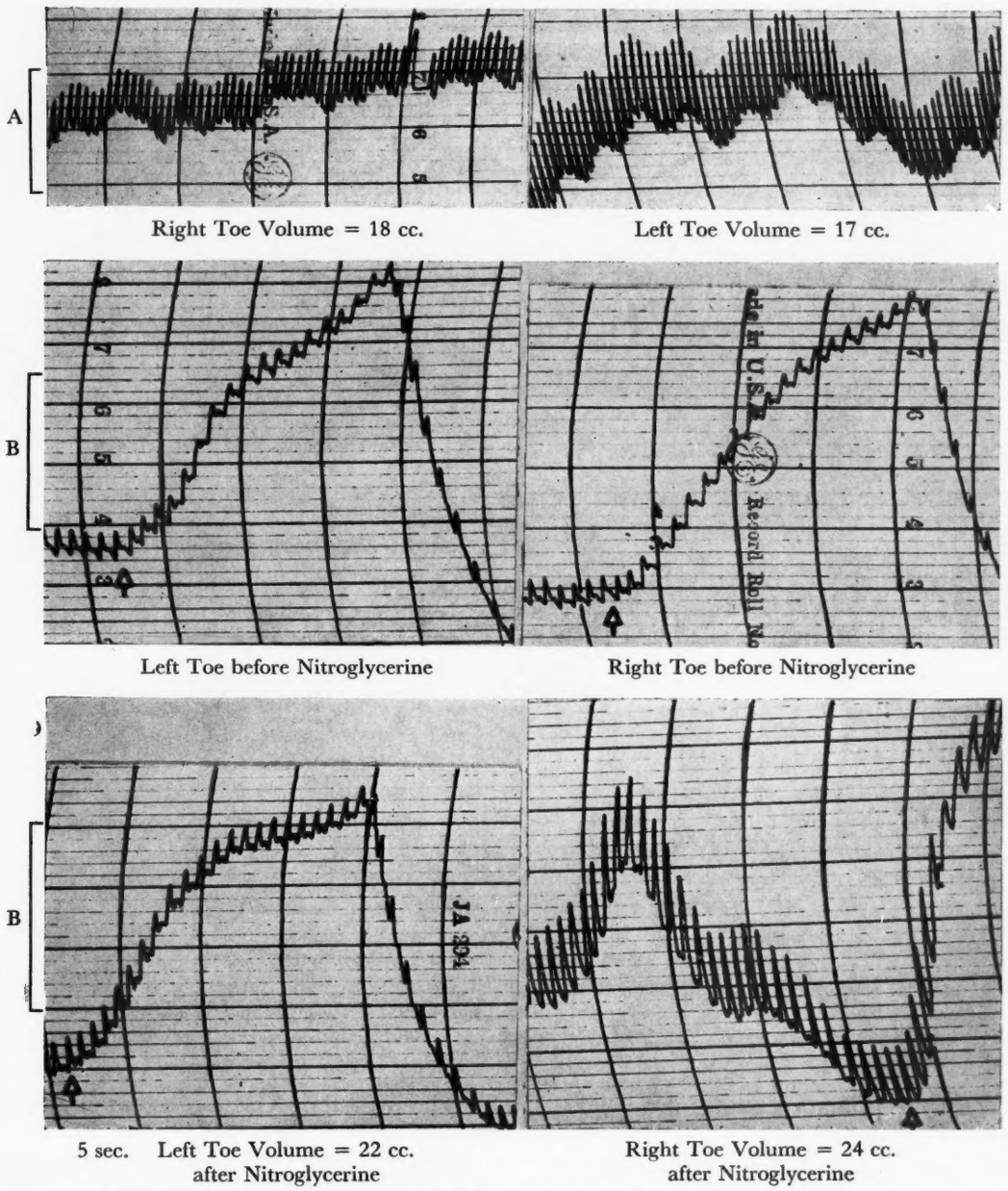


FIG. 3. Microplethysmograms from two diabetic patients (A and B). Tracings from patient A were obtained after nitroglycerine. Note the pronounced differences in the volume pulse amplitude in both great toes. The arrows on the tracings from patient B represent the onset of venous occlusion. Note that while the control tracings are identical, a marked disparity in pulse volume and blood flow developed following nitroglycerine. (Calibration to left of tracings = 20 cu. mm.)

this is the result of anatomic changes in the peripheral arteries.

The volume flow of blood through the digit represents the "end" circulation in an extremity.[8] A decrease in both digital blood flow and pulse volume signifies impaired circulation through the extremity without defining the nature or site of impairment. Some indication of the latter may be obtained by comparing the functional status of the proximal circulation with that of the distal peripheral circulation. This may be accomplished in part by correlating the oscillometric and the microplethysmographic findings. Thus an abnormal reduction in the oscillometric index denotes organic disease of the proximal arteries while a normal index

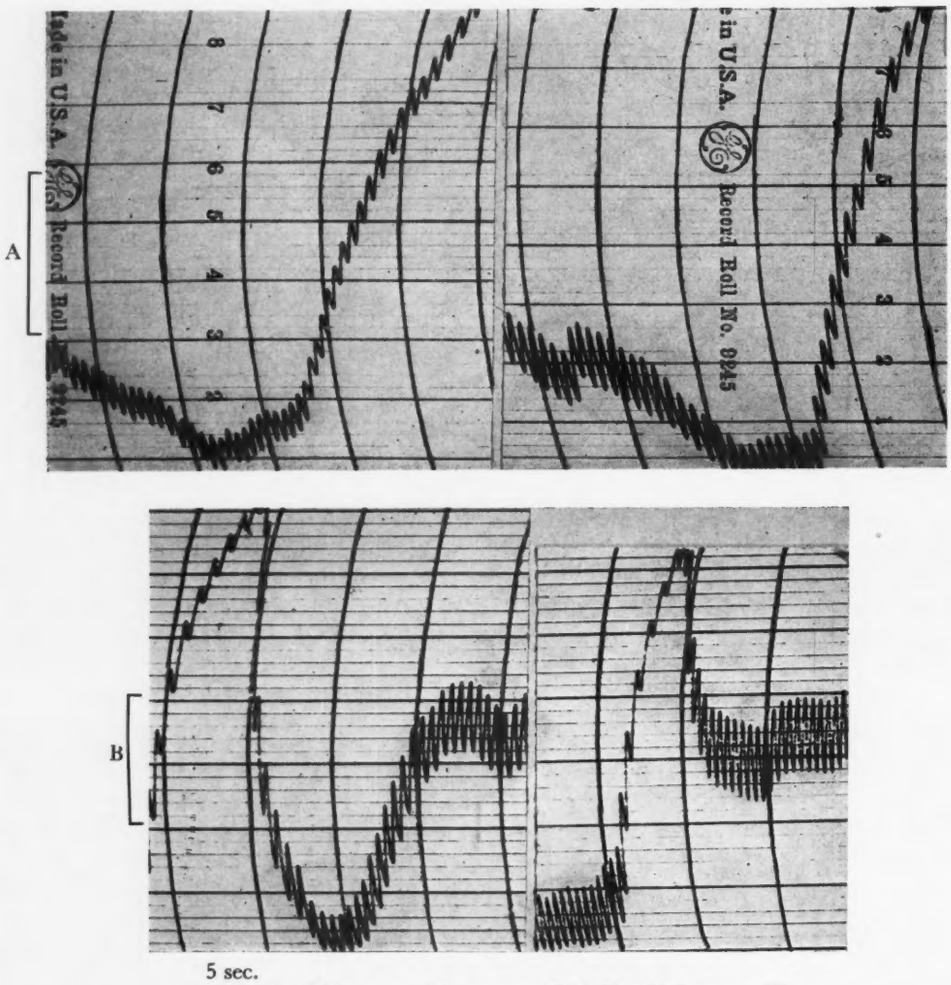


FIG. 4. Microplethysmograms from a diabetic patient. Note that the differences in pulse volume and blood flow which developed after nitroglycerine (A) disappear after tetraethylammonium blockade. (Calibration to left of tracings = 20 cu. mm.)

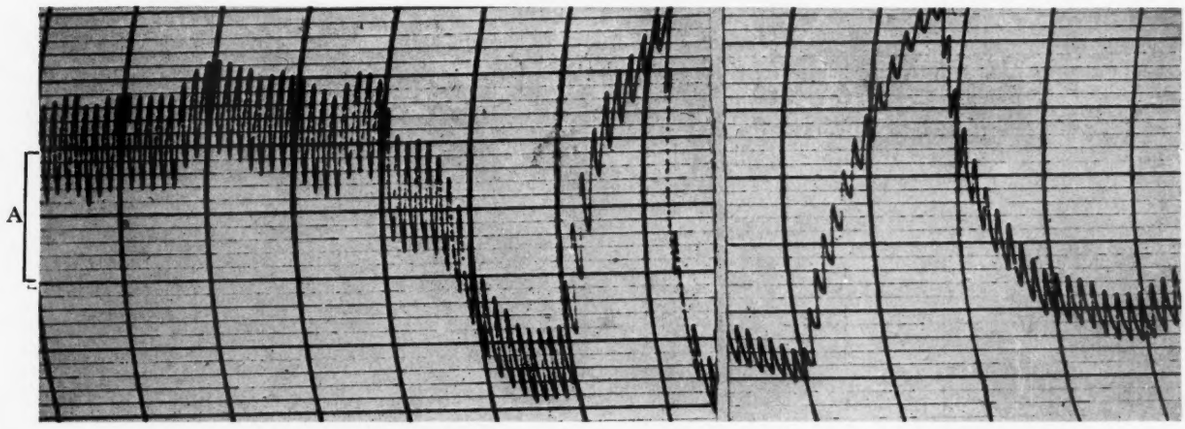
suggests that the primary vascular involvement is situated in the digital bed.

It was found that the oscillometric index as determined at three levels was normal bilaterally in all forty-seven patients. In view of the fact that both x-ray and physical examination of the lower extremities also were normal it is reasonable to assume the absence of significant or of extensive occlusive vascular disease up to and including the penultimate circulation. The validity of this premise is strengthened by the fact that a normal vasoconstrictor gradient was obtained in five of the fifteen patients who revealed microplethysmographic evidence of vascular disease. It should be noted parenthetically that this confirms the contention of Goetz that a normal skin temperature is not incompatible with the presence of organic vascular disease.[8]

By employing the microplethysmographic technic the existence of unsuspected occlusive digital vascular disease was thus discovered in fifteen of forty-seven diabetic patients. The statistical probability that the observed differences in digital blood flow and pulse volume are chance variations is less than 1:20,000. We have been unable to demonstrate similar differences in digital vascular patterns in comparable nondiabetic subjects.[9]

COMMENTS

Our studies cast doubt on the concept that diabetic peripheral vascular disease is merely a severe and accelerated variety of peripheral



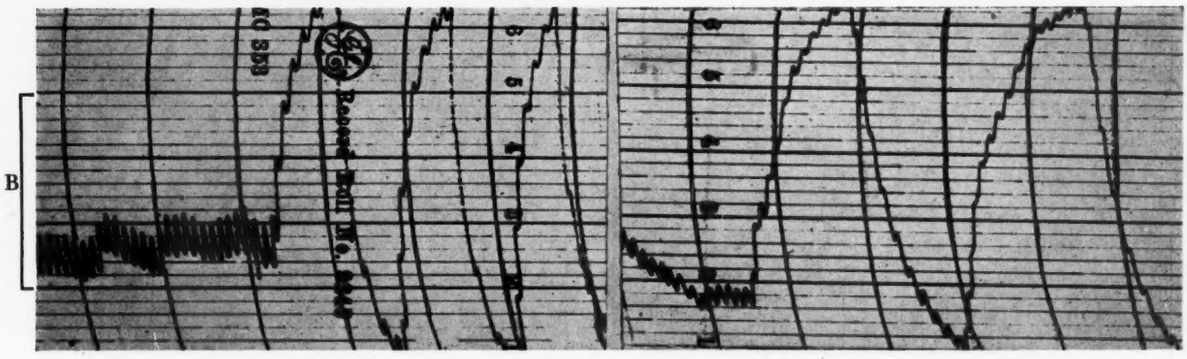


FIG. 5. Microplethysmograms from two diabetic patients (A and B). Note the persistent differences in blood flow and pulse volume following tetraethylammonium blockade. (Calibration to left of tracings = 20 cu. mm.)

arteriosclerosis. The microplethysmographic investigations indicate that occlusive digital vascular disease exists at a time when there is no other evidence to suggest the presence of peripheral arteriosclerosis. Furthermore, as has already been noted, comparable studies in normal individuals have not disclosed the changes in digital hemodynamics which have been observed in our diabetic patients. It is therefore hypothesized that the primary peripheral vascular lesion in diabetes mellitus is not arteriosclerosis but an occlusive angiopathy of the smallest vascular radicals. Although the histopathologic nature of the alterations is unknown, and although the primary localization of these lesions, whether in arteriole, capillary or venule, is undetermined, the physiologic end result is an obstruction of variable degree to the blood flow through the ultimate circulation. This in turn leads to increased resistance in the more central peripheral arterial bed. The anatomic expression of such hemodynamic change is accelerated vascular sclerosis. The fact that arteriosclerosis may be more advanced in one extremity suggests that the minute vascular lesions are distributed in an irregular patchy fashion and develop at a variable rate.

The alterations in the digital circulation as determined microplethysmographically, together with the characteristic lesions of diabetic retinitis and intercapillary glomerulosclerosis, suggest that the initial or fundamental vascular derangement in diabetes mellitus is limited to the smaller blood vessels. The fact that disease of the more minute channels develops in such diverse sites as the kidneys, the digits and the retinas implies that similar angiopathic disturbances might develop in other regions of the body such as the heart and brain.

The data offer no clues as to the mechanisms responsible for the vascular changes described. It is possible that abnormalities in lipid metabo-

TABLE I
MICROPLETHYSMOGRAPHIC DATA IN FORTY-SEVEN DIABETIC PATIENTS

No.	Sex	cPV		cBF		nPV		nBF	
		R	L	R	L	R	L	R	L
1.	F	4.5	4.5	12	13	5.5	12	11	41
2.	M	5	2	19	8	9	4	50	20
3.	M	6.5	3.5	22	10	18	5	60	22
4.	M	0.5	4	3	26	1.5	8	8	40
5.	F	4	5.5	17	55	7	6	13	70
6.	F	4.5	4	24	14	8.5	5	56	17
7.	M	5	2.5	25	4	10	3	72	10
8.	F	2	2.5	8	9	3	9	14	32
9.	F	3	7	12	36	4	9	16	42
10.	M	2	2	8	6	3.5	4	16	28
11.	F	2	5	6	18	3	9	10	42
12.	M	3	7	8	14	3	13	18	58
13.	F	8	3	42	10	18	6	62	20
14.	F	5	2	16	7	14	4	42	10
15.	M	6	3	18	9	11	7	28	18
16.	M	2.5	3.5	26	32	6	10	30	52
17.	M	2	12	8	45	4	12	20	50
18.	F	6	2	30	14	7	3	42	20
19.	F	11	4	48	16	18	7	64	22
20.	F	10	4	32	14	16	6	42	18
21.	M	2	6	8	18	3	10	10	26
22.	F	2	7	18	42	9	14	34	56
23.	M	10	11	30	38	17	17	62	66
24.	M	3	3	17	20	5	6	40	46
25.	F	8	7	45	50	16	13	64	60
26.	M	9	9	30	35	9	10	50	43
27.	F	8	13	52	60	13	13	68	64
28.	F	7	8	30	34	16	17	52	50
29.	F	3	3	28	22	10	9	46	40
30.	F	4	6	16	30	12	13	62	68
31.	M	10	9	17	15	17	15	72	64
32.	M	13	12	58	50	14	12	78	78
33.	F	9	8	56	46	16	15	74	66
34.	F	3	2	12	13	10	12	48	56
35.	F	6	8	40	52	12	13	64	70
36.	M	9	7	44	36	15	14	58	60
37.	M	6	10	26	28	10	10	40	34
38.	F	12	12	46	38	18	20	60	54
39.	M	6	7.5	24	20	10	9	38	30
40.	F	6	8	26	26	9	10	42	40
41.	M	5	5	44	38	16	15	48	50
42.	M	12	10	40	30	16	14	72	76
43.	F	10	6	32	20	12	11	44	38
44.	F	7.5	7	18	24	13	14	34	30
45.	F	5	7	15	18	16	15	52	46
46.	F	5	6	20	20	10	14	46	52
47.	F	9	8	26	18	12	11	30	24

cPV = control pulse volume in cm.; cBF = control blood flow in cc. per 100 cc. limb volume per minute; nPV = pulse volume after nitroglycerine; nBF = blood flow after nitroglycerine.

lism are associated intimately with the pathogenesis of the disease. Notwithstanding these possibilities, it should be re-emphasized that the intrinsic vascular abnormality of diabetes mellitus is an occlusive lesion of the minute blood vessels; that this defect should perhaps be considered as much a part of the diabetic syndrome as is the abnormality in carbohydrate metabolism; and that increased prevalence and accelerated development of arteriosclerosis in diabetes is linked directly to the increased intravascular tension imposed as a result of the lesions described.

TABLE II
ESSENTIAL DATA ON TWENTY-TWO DIABETIC PATIENTS WHO REVEALED MICROPLETHYSMOGRAPHIC ABNORMALITIES AFTER NITROGLYCERINE

No.	nPV		nBF		tPV		tBF	
	R	L	R	L	R	L	R	L
1.	5.5	12	11	41	7	20	20	86
2.	9	4	50	20	16	4	90	18
3.	18	5	60	22	28	7	100	32
4.	1.5	8	8	40	3	13	26	60
5.	7	6	13	70	7	8	18	94
6.	8.5	5	56	17	12	6	74	30
7.	10	3	72	10	16	4	104	36
8.	3	9	14	32	9	18	44	80
9.	4	9	16	42	5	10	42	70
10.	3.5	4	16	28	4.5	8	26	48
11.	3	9	10	42	5	16	24	66
12.	3	13	18	58	5	17	32	90
13.	18	6	62	20	24	10	88	40
14.	14	4	42	10	20	5	84	26
15.	11	7	28	18	13	8	50	32
16.	6	10	30	52	18	20	94	100
17.	4	12	20	50	14	15	84	90
18.	7	3	42	20	14	14	76	76
19.	18	7	64	22	24	23	82	78
20.	16	6	42	18	22	21	74	78
21.	3	10	10	26	16	17	62	66
22.	9	14	34	56	18	18	100	96

nPV = pulse volume after nitroglycerine; nBF = blood flow after nitroglycerine; tPV = pulse volume after tetraethylammonium; tBF = blood flow after tetraethylammonium.

SUMMARY

1. An evaluation of the peripheral circulation was made in a group of forty-seven diabetic patients, employing the microplethysmographic method. All patients were below the age of forty-five years.

2. Standard diagnostic technics failed to demonstrate any impairment of the peripheral circulation in each subject.

3. Using the response to nitroglycerine as a test method, twenty-two of the forty-seven patients showed significant differences in blood flow and volume pulse amplitude in one great toe as compared with the contralateral toe.

4. Following ganglionic blockade by tetraethylammonium, fifteen of these twenty-two patients continued to manifest significant reductions in flow and volume in one of the two halluxes.

5. These findings are considered to imply the presence of occlusive peripheral vascular disease in these subjects. In view of the normal oscillometric index, the disease is localized to the digital bed. Similar vascular alterations have not been demonstrated in non-diabetic patients of similar age groups.

6. It is suggested that the lesions in the digital bed are analogous to the vascular lesions of diabetic retinitis and intercapillary glomerulosclerosis, and constitute an integral manifestation and not a secondary complication of diabetes mellitus.

7. The increased proximal resistance which will follow upon the development of a more distal occlusive angiopathy is considered to account, at least in part, for the increased incidence and accelerated development of clinical arteriosclerosis in diabetes.

8. The alterations in the minute digital blood vessels appear to represent a vascular change distinct from the usual type of peripheral arteriosclerosis.

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Nor-epinephrine; Effect in Normal Subjects; Use in Treatment of Shock Unresponsive to Other Measures*

JOHN H. MOYER, M.D., JAMES M. SKELTON, M.D. *and* LEWIS C. MILLS, M.D.
Houston, Texas

THERAPEUTIC agents for the treatment of shock have been searched for over a great many years. Blood, plasma, fluid replacement therapy and measures directed to correct the etiology of the shock have comprised the primary and most satisfactory treatment. Although these measures when used properly have been satisfactory in most cases, there are a number of patients in whom the shock state persists with subsequent death. These patients do not respond to administration of fluids which may, indeed, be contraindicated. This is especially true in shock resulting from such non-surgical causes associated with absolute or chronic congestive heart failure. Even "surgical shock," when it has existed for prolonged periods, may not respond to fluid replacement therapy and corrective surgery. This has been well documented experimentally in animals in which shock following blood loss becomes irreversible after prolonged periods of time, despite transfusion of more blood than was originally removed. Under these circumstances, further fluid administration also will be valueless and is, therefore, contraindicated since it may lead to acute herat failure and pulmonary edema.

Undoubtedly a large factor in the production of the so-called "irreversible shock state" is damage to the brain and other vital organs as a result of inadequate perfusion pressure during the period of hypotension. It is inescapable that the sooner one returns the blood pressure to a level adequate for perfusion of these vital organs the more likely the patient is to recover, provided he does not die from the primary disease process which is responsible for the shock. Therefore, an agent is needed which will consistently raise the blood pressure when other measures fail. For these purposes an agent with the following characteristics would be desirable: (1) one which would raise blood pressure rapidly in a majority of patients regardless of the cause of the hypotension, until the patient's own vasopressor mechanisms stabilize and maintain the blood pressure or, in the case of untreated surgical shock, until specific measures can be instituted, i.e., blood transfusion started, ligation of a bleeding vessel, etc.; (2) an agent whose effects could be easily controlled so that one could obtain any desired blood pressure response; (3) a short-acting agent, so that the pressor effect of therapy could be terminated at any time or, if the blood pressure were accidentally elevated to excessive levels, this would persist only for a very short time and (4) an agent with minimal side effects.

Nor-epinephrine† is a drug which seems to meet most of these criteria. It is a drug closely related to epinephrine, differing only in the absence of the N-methyl group but having different pharmacologic properties in that it is primarily a peripheral vasoconstrictor and has only a minimal stimulant effect on the heart. For this reason a project was undertaken to study some of the pharmacodynamic properties of this drug in a group of normal individuals, and also its effectiveness in the treatment of various kinds of shock. The results of this study comprise the basis of this report. Preliminary observations have been presented previously.[1,2]

METHODS AND PROCEDURES

Normal Subjects. Twenty-five normotensive patients were selected from the outpatient department and hospital wards. Twenty patients

† Levophed supplied by Winthrop-Stearns, Inc.

* From the Departments of Medicine and Pharmacology, Baylor University College of Medicine, Houston, Tex.

received a single subcutaneous injection of nor-epinephrine (average 6 γ/kg.). Five were given the drug by continuous intravenous infusion. During the control period, which was usually twenty to forty minutes in duration, the blood pressure, pulse rate and respiration were checked every minute for the first five minutes and every two to five minutes thereafter until they had returned to the control levels. In eight of the patients the vital capacity, circulation time (decholin®), hematocrit and blood sugar (Folin and Wu) were determined during the control period, during the height of the pressor effect, and after the blood pressure had returned to the control level. In ten patients electrocardiograms were made during these same periods. In the five patients who received a continuous intravenous infusion of nor-epinephrine (4 mg./L. of 5 per cent glucose in distilled water), the blood pressure was elevated to and stabilized at hypertensive levels and was checked every five minutes. Electrocardiograms and ballistocardiograms were made during the control period and after the blood pressure was stabilized at hypertensive levels. The latter will be included in a separate report.

Patients in Shock. Nor-epinephrine was administered by constant intravenous infusion to forty-four patients with shock not responding to other measures. The concentration of nor-epinephrine usually was 4 mg. per L. of 5 per cent glucose in water. In some patients who did not have an adequate pressor response to this concentration, it was increased to as much as 24 mg. per L. in order to avoid excessive fluid administration. The rate of infusion varied in accordance with the patient's blood pressure. A constant watch was kept on all the patients in order to keep the blood pressure within the normal range. Repeated electrocardiographic determinations were made whenever possible.

The forty-four patients in shock included fourteen with myocardial infarction, nine with overwhelming infection, six with excessive hypotension secondary to medication and fifteen cases of surgical shock (postoperative shock, shock following hemorrhage, transfusion reaction and trauma). All of the surgical patients had previously failed to respond to adequate fluid replacement and blood transfusions. With the exception of the hypotension following medication, these patients would have been classified as "irreversible shock" if a vasopressor agent had not been available.

RESULTS

Observations on Normal Patients. In the twenty normal patients who received subcutaneous injections of nor-epinephrine a vasopressor effect was noted within the first one to five minutes.

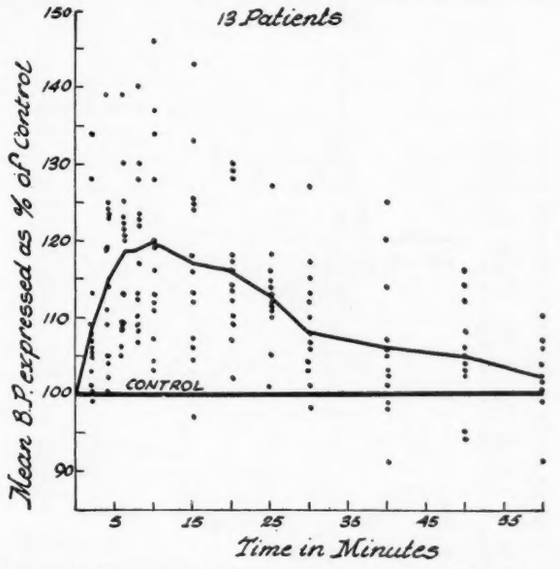

FIG. 1A. The mean blood pressure after administration of nor-epinephrine subcutaneously is expressed as per cent of that found in the control observation and is plotted against time for each of thirteen patients. The solid line represents the average of the thirteen observations at each time interval.

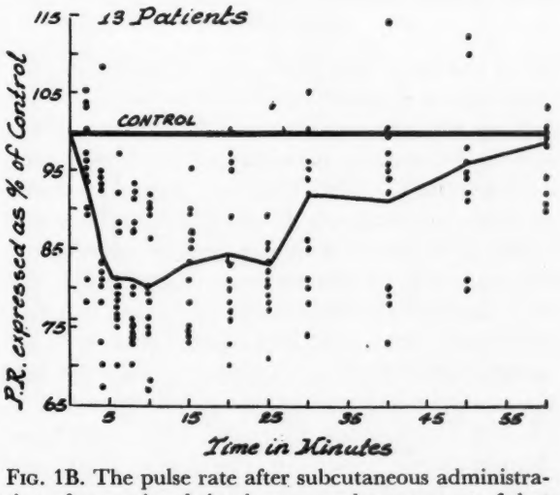

FIG. 1B. The pulse rate after subcutaneous administration of nor-epinephrine is expressed as per cent of that found in the control observation for each thirteen patients. The solid line represents the average for the thirteen patients.

The duration of significant hypertensive response was from fifteen to sixty minutes. Figures 1A and B show the pulse rate and mean blood pressure response (one-third pulse pressure plus diastolic pressure) to subcutaneous nor-

epinephrine when given to thirteen normal patients. The values are expressed as per cent of the control observations. Seven patients are not included in this graph because the blood pressure was not followed until it had returned to the control levels. (Figs. 1A and 1B.) A typical

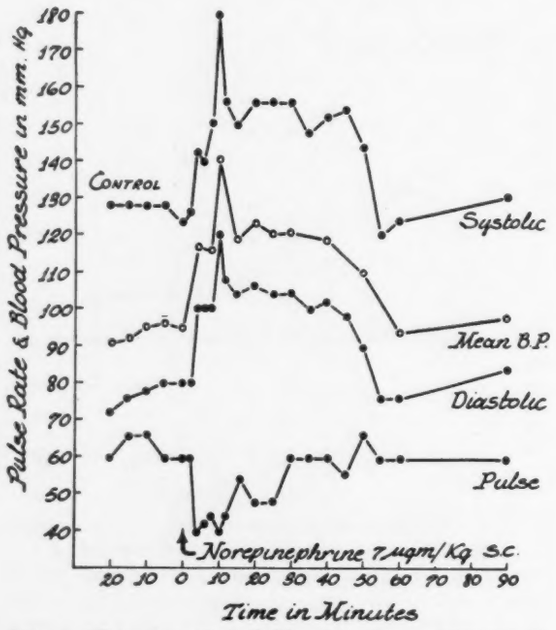

FIG. 2. This is a typical blood pressure response to subcutaneous nor-epinephrine (7γ/kg.).

blood pressure and pulse rate response to nor-epinephrine is presented in Figure 2.

Following the increase in blood pressure there was no subsequent vasodilatation (blood pressure reversal). The diastolic blood pressure increased (average = 38 per cent) to an extent equal to or more than the systolic blood pressure (average = 22 per cent). The pulse rate was consistently decreased (average decrease = 23 per cent). The circulation time was not altered significantly. (Table 1.) The average hematocrit for the group increased from 40.5 to 46 (12.5 per cent increase). No significant changes were noted in respiratory rate and depth, vital capacity or the concentration of blood glucose.

There was an immediate pressor response (within 10 to 30 seconds) in the five normal patients who received nor-epinephrine intravenously. (Fig. 3.) The blood pressure could be regulated at any desired level by varying the rate of infusion. Here, too, there was a consistent decrease in pulse rate which varied inversely to the increase in blood pressure. The bradycardia could be blocked with atropine without affecting the blood pressure. Figure 3 illustrates a typical pressor response to an intravenous infusion of nor-epinephrine and contrasts it with the response to a similar infusion of epinephrine.

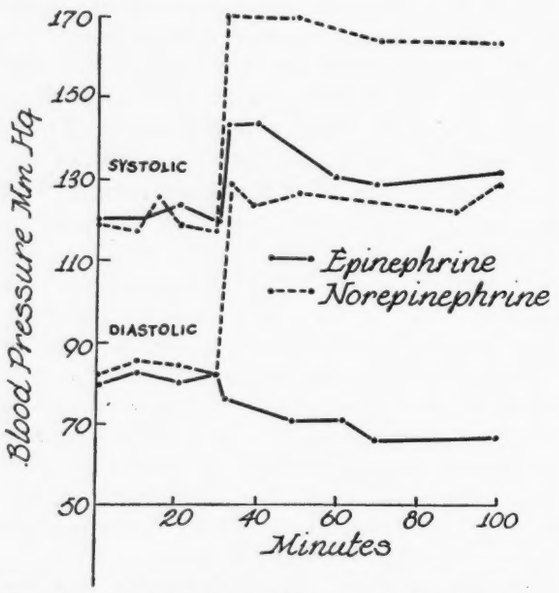

FIG. 3. This illustrates the difference in blood pressure response between an intravenous infusion of epinephrine and nor-epinephrine. The systolic pressure increase is prominent after both epinephrine and nor-epinephrine. However, after nor-epinephrine the diastolic rises as much as or more (percentagewise) than the systolic. By contrast, after epinephrine the diastolic pressure changes very little or may decrease.

The marked increase in diastolic pressure is in direct contrast to the response to epinephrine. There was a significant rise in blood glucose concentration following intravenous nor-epinephrine (average 40 per cent increase) which was not seen following the subcutaneous route of administration.

In fifteen normal patients (ten after subcutaneous injection; five after intravenous injection) in whom electrocardiographic determinations were made, the tracings before medication were uniformly normal. Following nor-epinephrine, in addition to bradycardia, three subjects showed definite changes in rhythm which consisted of a shift of the site of impulse formation from the SA node to another site in the auricle, nodal or auricular premature contractions and heart block. Subject 1 showed a progressive increase in auriculoventricular conduction

(Wenckebach phenomenon). These changes were transient in nature and returned to normal about the time the blood pressure returned to the control level. No ventricular premature contractions were noted.

Side effects to both subcutaneous and intravenous nor-epinephrine were minimal. Headache occurred if the pressure was markedly increased. Slight blanching of the skin and a local pilomotor response was noted in some of the subjects at the site of subcutaneous injection.

Observations on the Intravenous Infusion of Nor-epinephrine to Patients in Shock. Of the forty-four patients treated for shock only two failed to have an initial pressor response. The others had a prompt rise in blood pressure within ten to sixty seconds after the infusion was started and it was possible to maintain the blood pressure at any desired level by varying the rate of infusion. The two patients who failed to respond were in extremis prior to receiving the drug. One of these (No. 4, Table II) was admitted to the hospital because of a third myocardial infarction. She had been in shock for an undetermined period of time prior to treatment with nor-epinephrine. The other patient who failed to respond was in severe congestive failure with peripheral circulatory collapse. The blood pressure was unobtainable for at least forty-five minutes prior to treatment with nor-epinephrine and death was imminent.

Twenty-four of the forty-two patients who showed a pressor response recovered from shock and nor-epinephrine was discontinued. The other eighteen patients died in spite of the fact that their blood pressures could be maintained at normal levels with nor-epinephrine until just prior to death. Five of the patients who died required increasing amounts of nor-epinephrine to maintain an adequate pressor response and in three of these the concentration of the solution had to be increased to 24 mg. of nor-epinephrine per L. Serial electrocardiograms were made in all cases of myocardial infarction both before and after treatment and in all other cases when practical. Except for a decrease in heart rate there were no electrocardiographic changes attributable to nor-epinephrine.

When the shock had persisted for more than two hours, all patients were either anuric or severely oliguric. Of those who responded to nor-epinephrine only four patients failed to have an increase in urinary output to 1,000 cc. or more daily. One of the four patients who failed to have an increase in urinary output developed a lower nephron nephrosis and died in uremia. Of the remaining three, one patient was anuric and the other two excreted less than 800 cc. of urine prior to death from the shock state.

TABLE I
COMPARING RESPONSES TO NOR-EPINEPHRINE WHEN ADMINISTERED SUBCUTANEOUSLY AND INTRAVENOUSLY

	Intravenous*		Subcutaneous	
Onset of action	15″		2′30″†	
Duration of action	60″ after discontinuing		34′15″†	
	Control	Drug	Control	Drug
Blood pressure	119/76	191/105	130/77	158/106
Pulse rate	70	52	73	56†
Hematocrit	38	41	40.5	46‡
Blood sugar	94 mg. %	132 mg. %	87 mg. %	87 mg. %‡
Vital capacity	.....	.....	4.4 L.	4.3 L.‡
Circulation time (decholin)	.....	.....	16 sec.	18 sec.‡
Side reactions	Frontal headache		Frontal headaches—2 patients; not severe	

* Average values for five patients.
† Average values for twenty patients.
‡ Average values for eight patients.

The patients treated for shock have been placed in four groups for purposes of more detailed presentation: (1) shock secondary to myocardial infarction; (2) shock associated with overwhelming infection; (3) excessive hypotension following medication and (4) shock associated with postoperative or surgical complications.

Myocardial infarction: Table II summarizes the data on fourteen patients in shock due to myocardial infarction. The diagnosis was confirmed by electrocardiographic tracings. In those patients who died the diagnosis was corroborated at autopsy in all cases but one. Postmortem examination of this patient showed severe coronary arteriosclerosis and aortic stenosis. The patient died within two hours after the onset of the acute shock state which may have accounted for the absence of definite pathologic evidence of infarction.

The prognosis in all fourteen patients in this group appeared hopeless prior to treatment

with nor-epinephrine. Schnur[3] in the same hospital found a 97 per cent mortality in patients who were observed under similar conditions but were not given a vasopressor drug. The severity of the shock can be estimated by

pressure remained at normotensive levels in six patients after therapy was discontinued. During nor-epinephrine therapy there was no change in rhythm, either clinically or by electrocardiogram. In five patients digitalis was given in

TABLE II

PATIENTS TREATED WITH NOR-EPINEPHRINE BECAUSE OF SHOCK DUE TO MYOCARDIAL INFARCTION

No.	Hours of Shock Prior to Treatment	Initial*		During Treatment		EKG† Changes	Hours of Treatment	Results and Remarks
		Pressure	Pulse	Pressure	Pulse			
1	2	Unobtainable	100	110/70	70	None	4	Good initial response; required progressively larger doses; sudden collapse and death
2	½	60/?	140	120/100	130	None	20	Had second myocardial infarction; became unresponsive to nor-epinephrine and died with severe left ventricular failure
3‡	1	60/0	150	110/70	90	None	6 4	Shock on two occasions; responded to nor-epinephrine each time and blood pressure remained normal after discontinuance
4	?	40/?	160	40/?	160	None	12	No pressor response; patient died
5	3	70/50	126	100/70	100	None	72	B.P. maintained at normal levels; received digitalis and mercuhydrin; died in congestive failure
6‡	?	Unobtainable	?	140/110	90	None	3 3 6	Responded to nor-epinephrine; pressure normal after discontinuing drug third time
7	¾	Unobtainable	140	Unobtainable	140	None	1½	No effect; severe congestive failure; died
8	½	60/40	130	110/70	110	None	¾	Died
9	4	Unobtainable	?	110/80	120	None	48	Rapid auricular fibrillation; digitalis and quinidine used in conjunction; recovered
10	48	40/10	128	110/90	92	None	96	Anuric prior to nor-epinephrine; slight output after therapy begun but developed a lower nephron nephrosis; died in uremia
11†	2	50/0	136	100/80	114	None	48	Good pressor response in each episode of shock; recovery uneventful
12	12	70/20	128	106/64	92	None	36	Complete recovery
13	2	20/?	152	92/62	99	None	6	Died of congestive failure; received digitalis and mercuhydrin
14	1	60/40	160	130/80	120	None	2	Rapid auricular fibrillation; blood pressure stabilized at 130/80; rhythm converted to sinus by quinidine; recovered

* Determinations just prior to treatment.
† Changes from pretreatment tracings other than those attributable to myocardial infarction.
‡ Nor-epinephrine used only when blood pressure dropped below 85 mm. Hg systolic.
B.P.—Blood pressure.

referring to the blood pressure determinations recorded in Table II. The duration of shock prior to treatment varied from thirty minutes to forty-eight hours.

The duration of treatment varied from forty-five minutes to ninety-six hours. The blood

conjunction with nor-epinephrine because of concurrent congestive failure.

ILLUSTRATIVE CASE REPORTS

CASE 6. L. G., a forty-one year old Negro female, was admitted to the hospital with the

TABLE III

PATIENTS TREATED WITH NOR-EPINEPHRINE BECAUSE OF SHOCK DUE TO OVERWHELMING INFECTION OR REACTION TO MEDICATION

Diagnosis	Hours of Shock	Pretreatment*		Treatment		Hours of Treatment	Results and Remarks
		Pressure	Pulse	Pressure	Pulse		
A. Patients with Shock Associated with Infection							
15. Pneumonia, pulmonary edema	24	50/0	140	130/40	88	20	Good pressor response; continued to require progressively larger doses until death from infection
16. Pneumonia, pulmonary edema	6	70/56	120	130/90	100	8	N.E. discontinued after 8 hr. with B.P. remaining at normal levels
17. Pneumonia	2	40/?	154	120/76	132	48	Died with progressive disease not responding to antibiotics despite normal B.P.
18. Meningococcemia	24	60/40	150	120/80	130	24	Developed signs of pulmonary edema and died
19. Meningococcemia	4	80/60	130	110/80	88	14	Sudden loss of pressor response at 14 hr. and died of infection
20. Meningococcemia	8	30/10	148	110/80	110	48	N.E. discontinued after 48 hr. with pressure remaining normal; recovered
21. Acute endocarditis	3	Unobtainable	138	100/72	90	96	Used intermittently for 96 hr. as required; recovered
22. Acute hepatitis	½	50/30	138	110/74	100	2	Progressively larger doses; died of infection
23. Acute hepatitis	2	60/30	92	110/80	88	15	Sudden loss of pressor response; died of infection
B. Patients with Shock Secondary to Medications							
24. Acute hypertensive crisis	½	Unobtainable	?	160/110	100	2	Marked hypotension after hexamethonium; responded to N.E. Pressure remained elevated after discontinuance
25. Hypertension	48	85/70	90	150/90	84	24	Hypotensive response to hexamethonium; anuric for 48 hr. Complete recovery† with N.E.
26. HCVD	⅙	50/0	48	142/92	54	2	Excessive hypotensive response to I.V. veriloid; EKG showed transient A-V dissociation; recovered with N.E.
27. HCVD	1	40/0	32	118/72	58	4	Excess vasodepression due to I.V. Veriloid; complete recovery
28. ASHD, HCVD	1	Unobtainable	?	110/70	90	5	Vasodepression due to I.V. aminophylline; complete recovery
29. ASHD	⅙	Unobtainable	?	110/80	78	6	Vasodepression due to I.V. mercuhydrin; complete recovery

* Determinations just prior to treatment.
† See Figure 4, Case report No. 24.
HCVD—Hypertensive cardiovascular disease.
ASHD—Arteriosclerotic heart disease.
N.E.—Nor-epinephrine.
B.P.—Blood pressure.
I.V.—Intravenously.

diagnosis of arteriosclerotic and hypertensive cardiovascular disease with congestive failure, acute myocardial infarction and peripheral circulatory collapse. The patient first developed heart failure three months previously. In spite of digitalization and bed rest she had become progressively worse. When first seen in the hospital she was in profound shock. The pulse and blood pressure were unobtainable. There was acute dyspnea with an apical heart rate of 140, bilateral basilar rales, an enlarged tender liver and peripheral edema. The electrocardiogram showed the changes of acute anterior myocardial infarction. The patient was given oxygen, intravenous digitalis and intravenous mercuhydrin. Because of the shock she was given an infusion containing 4 mg. of nor-epinephrine in 1,000 cc. of 5 per cent glucose in distilled water. There was an immediate rise in blood pressure and it was maintained at about 140/110. The pulse rate ranged between 90 and 96. It was necessary to continue the nor-epinephrine infusion for approximately three hours. The patient was placed on anticoagulants and appeared to do well for four days. On the fourth hospital day she once again developed sudden shock, probably due to a pulmonary infarction. The blood pressure was unobtainable. Again an infusion containing 4 mg. of nor-epinephrine in 1,000 cc. of 5 per cent glucose in distilled water was given intravenously with an immediate response in blood pressure to 160/100. After discontinuing nor-epinephrine for two hours the blood pressure remained between 100/70 and 90/60. Serial electrocardiograms during this period showed the evolutionary pattern of an anterior myocardial infarction and digitalis effect. Two weeks later she had another episode of severe shock which responded to nor-epinephrine. The drug was given over a six-hour period during which time shock supervened whenever the infusion was discontinued. After this period of time the nor-epinephrine was discontinued and the blood pressure stabilized at 110/80.

Case 9. W. T., a fifty-eight year old Negro man, was admitted to the hospital in profound shock. There was a previous history of arteriosclerotic and hypertensive cardiovascular disease and the patient had been receiving digitalis. The blood pressure three hours prior to admission was 160/100. Physical examination on admission revealed an acutely ill Negro man with an unobtainable blood pressure. Serial electrocardiograms before and after treatment revealed rapid auricular fibrillation and right bundle branch block. Nor-epinephrine was administered slowly by intravenous infusion and after forty minutes the blood pressure was 80/50. The blood pressure was finally stabilized at 110/80. Treatment was continued for forty-eight hours before nor-epinephrine could be discontinued. Quinidine was given intravenously during this period without altering the auricular fibrillation. The patient was ultimately discharged from the hospital on digitalis, quinidine and low sodium diet.

Shock secondary to overwhelming infection and medications: There were nine patients treated for shock due to overwhelming infection. (Table III.) The duration of shock varied from thirty minutes to twenty-four hours and treatment from two hours to ninety-six hours. All nine patients had an adequate pressor response but only three patients recovered. In two patients in this group it was necessary to use infusions containing as much as 24 mg. of nor-epinephrine per L. in order to maintain an adequate pressor response.

The six patients with acute hypotension secondary to medications recovered. (Table III.) All of these patients had arteriosclerotic or hypertensive cardiovascular disease. Duration of treatment was shorter than in any other group and smaller amounts of nor-epinephrine were needed.

ILLUSTRATIVE CASE REPORTS

Case 18. C. R., a fifty-nine year old white man, was admitted to the hospital with meningococcemia, meningitis and a blood pressure of 75/60. In spite of penicillin, gantrisin, whole blood, cortisone and lipo-adrenal extract, the blood pressure fell to 60/40 at the end of the first hospital day. Nor-epinephrine (4 mg. per L. of 5 per cent glucose in distilled water) was given intravenously with an immediate increase in blood pressure to 124/80, which could be maintained at this level for twenty-four hours; however, increasing amounts of nor-epinephrine were required. The urinary output was low (840 cc. in twenty-four hours). The patient suddenly developed signs of pulmonary edema and died, although the blood pressure was maintained until death.

Case 25. D. O., a forty-three year old white female, was admitted to the hospital because of progressive hypertension. The blood pressure

TABLE IV

PATIENTS TREATED WITH NOR-EPINEPHRINE FOR SHOCK DUE TO OPERATIVE OR POSTOPERATIVE COMPLICATIONS

Diagnosis	Hours of Shock	Initial*		During Treatment		Hours of Treatment	Results and Remarks
		Pressure	Pulse	Pressure	Pulse		
30. Ruptured viscus	2	Unobtainable	?	112/100	140	5	Good pressor response; died of peritonitis
31. Postoperative peritonitis	3	Unobtainable	?	100/80	144	38	Required progressively larger doses; died from infection
32. Postoperative	24	40/20	120	120/80	80	96	Anuric prior to and for 8 hr. after treatment instituted; complete recovery†
33. Postoperative	12	80/60	120	132/78	104	2.5	Shock 12 hr. following therapeutic abortion, complete recovery
34. Postoperative	2	20/?	164	90/48	148	1	Shock following splenectomy; died, cause undetermined
35. Postoperative	6	50/20	118	116/72	102	32	Developed lower nephron nephrosis (mild); recovery complete
36. Postoperative	½	20/?	138	198/78	112	96	Complete recovery
37. Postoperative transfusion reaction	½	Unobtainable	?	110/80	120	18	Initially anuric; urinary output 1,200 cc. after treatment with N.E., progressive icterus; died
38. Hemorrhage and transfusion reaction	1	Unobtainable	180	110/85	145	5	Complete recovery
39. Traumatic	12	50/20	134	110/70	70	72	Complete recovery
40. Massively bleeding peptic ulcer	2	Unobtainable	150	130/80	70	3	After pressure had stabilized a subtotal gastrectomy was performed; recovered
41. Hemorrhagic pancreatitis	2	78/58	100	180/110	76	9	Adm. pressure 270/130; developed pulmonary edema and shock; digitalized with slowing of pulse rate; became anuric and died despite normal B.P.
42. Traumatic hemothorax, ruptured	½	Unobtainable	?	130/110	120	15	Cardiac arrest 3 times on operative table; restored with massage, $CaCl_2$ and epinephrine, B.P. maintained by N.E. until death
43. Hemorrhagic pancreatitis	2	50/20	142	114/70	90	30	Collapse following paravertebral block; recovery uneventful
44. Gunshot wound	4	50/0	136	120/90	78	72	Temperature 107°F., recovered

* Just prior to treatment.

† Case report 32, see Figure 5.

Blood volume was previously corrected in all patients without recovery from shock.

was 180/120. She was given hexamethonium and the dose increased until she was taking 750 mg. four times per day. Following this she had a marked hypotensive response and the blood pressure decreased to 85/52 and remained at this level for two days. On the second day she became anuric. An infusion of nor-epinephrine was started with a prompt rise in blood pressure to normotensive levels. After about an hour she began to excrete urine and the subsequent twelve-hour output was 1,800 cc. (Fig. 4.) Glomerular filtration rate was determined before hexameth-

onium was administered and after the administration of nor-epinephrine. Glomerular filtration rate could not be determined during the hypotensive phase because of the anuria.

Surgical shock: Table IV summarizes the course in those patients with shock occurring postoperatively or due to some surgical complication. There were fifteen patients in this group. In all cases blood volume had been corrected without recovery from shock prior to the use of nor-epinephrine. The duration of shock varied from twenty-five minutes to twenty-four hours and treatment from one to ninety-six hours. The blood pressure returned to normal levels in all patients in this group. Complete recovery occurred in nine of fifteen patients.

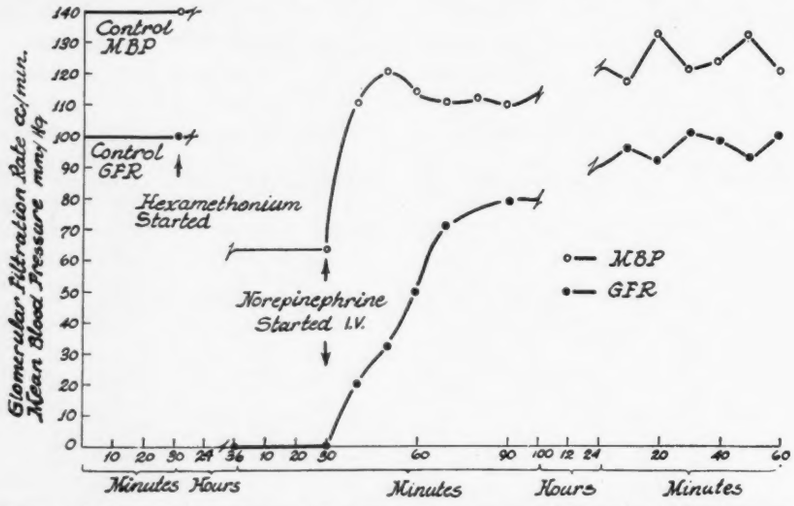

FIG. 4. This graph presents the observations on renal function following an excessive hypotensive response to hexamethonium. During the hypotensive phase the patient was anuric. Following an increase in blood pressure with nor-epinephrine there was an increase in urine output and the glomerular filtration rate gradually returned to the control level. (*Courtesy of J. Clin. Investigation.*)

ILLUSTRATIVE CASE REPORTS

CASE 32. A. B., a thirty-five year old Negro woman, was admitted to the gynecologic service for an abdominal hysterectomy. The history and physical examination were essentially normal except for uterine fibroids. The blood pressure was 130/90 and the pulse rate was 84. During the operation the blood pressure fell to 60/40 but the immediate postoperative blood pressure was 120/70. In spite of 1,000 cc. of whole blood and 500 cc. of plasma, the blood pressure again decreased to 64/42 at the end of the first postoperative day. The following morning the blood pressure was 60/26. One thousand cc. of blood was given without benefit and the blood pressure decreased to 40/20. An infusion containing 4γ per cc. of nor-epinephrine was begun and within five minutes the blood pressure was 108/80 and it was maintained at this level. All attempts to discontinue nor-epinephrine resulted in an immediate drop in blood pressure to unobtainable values but there was an immediate resumption of pressor effect on continuing therapy. (Fig. 5.) Further blood transfusions were given without benefit. During the day the patient received 4 L. of nor-epinephrine solution and after having been anuric for eighteen hours began to excrete small amounts of urine. Urinary output the following day was 1,600 cc. On the third day of therapy nor-epinephrine was discontinued for almost one hour but the pressure dropped to 55/40, necessitating continuance of the infusion for the remainder of that day. On the third postoperative day the sclerae became icteric. Her temperature rose to 108°F. but the patient was conscious and urinary output remained adequate. On the third and fourth day of nor-epinephrine therapy it was necessary to infuse only about 1 cc. per minute in order to maintain the blood pressure, whereas previously it had taken 4 to 5 cc. per minute. Only after eighty-six hours of almost continuous therapy with nor-epinephrine was it possible to omit it. Four weeks later the patient was discharged from the hospital in good health.

CASE 40. E. E., a fifty-nine year old white woman, was admitted to the hospital with shock due to a bleeding peptic ulcer. She also had arteriosclerotic heart disease. The shock was adequately controlled by a blood transfusion and she was subsequently placed on an ulcer regimen. After a recurrent episode of hematemesis several days later her blood pressure dropped from 80/60 to unobtainable levels. Intravenous nor-epinephrine was begun while awaiting blood for replacement therapy. However, in spite of 1,200 cc. of whole blood she required nor-epinephrine for a three-hour period prior to stabilization. A subtotal gastrectomy was performed that night and the subsequent course was uneventful.

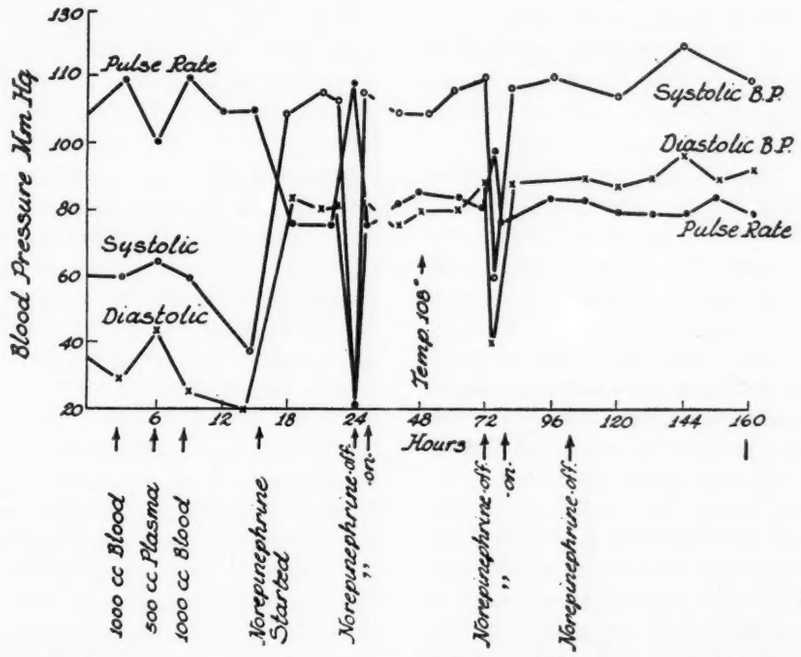

FIG. 5. Blood pressure response to nor-epinephrine infusion. See text for description of case (Patient No. 32-A.B.).

COMMENTS

Pharmacology. Nor-epinephrine has been demonstrated to be present normally in mammalian adrenergic nerve fibers,[4] in normal adrenal glands[5] and in pheochromocytomas.[6,7] It has been isolated from natural U.S.P. epinephrine.[8] As with epinephrine, the levoisomer has been shown to be the most physiologically active form.[9] The vasopressor effect of nor-epinephrine differs from epinephrine (Fig. 3) in that the predominant action is arteriolar constriction. Since epinephrine produces tachycardia, increased cardiac output and decreased peripheral resistance,[10] there is an elevation of the systolic blood pressure but the diastolic pressure usually remains the same or decreases.[11] The mean blood pressure is usually only slightly elevated. Contrariwise, following the administration of nor-epinephrine there is an increase in peripheral resistance[10,12–15] without a significant increase in cardiac output. As a result there is a marked rise in diastolic as well as systolic blood pressure. This hemodynamic response closely resembles that seen in essential hypertension, which has led to the suggestion by some authors that nor-epinephrine may be involved in the etiology of this disease.[11,14] Nor-epinephrine produces a moderate elevation of the hematocrit without producing any change in the circulating blood volume.[16] Bradycardia consistently follows the rise in blood pressure, probably due to stimulation of the carotid sinus reflex.[10,12] Experimentally, the drug has been shown to lower the threshold of irritability of papillary muscle.[17] However, Nathanson[18] believed that the drug had very little effect on the irritability of the ventricle. The occurrence of ectopic rhythms arising from auricular foci but not from ventricular foci in several of the normal subjects in the present study seems to confirm this observation.

Although the hyperglycemic effect of nor-epinephrine is much less than that of epinephrine,[10,20–22] the present studies indicate that the blood sugar can be increased significantly by intravenous infusions of this drug. It has very little central nervous system stimulating action and the eosinopenic response which is seen after epinephrine is absent.[10,21] However, if the vasopressor response of nor-epinephrine is blocked with dibenzyline so that larger doses are feasible, a rather marked central nervous system stimulant effect can be demonstrated.[23]

Clinical Uses. The observations on the cardiovascular response of normal individuals to nor-epinephrine are in general agreement with those of other investigators. The greater percentage increase in diastolic than in systolic blood pressure (Table I) is compatible with a primary increase in peripheral resistance in the absence of a significant increase in cardiac output. Because of this specificity for increasing the blood pressure by peripheral vasoconstriction, nor-epinephrine is particularly useful in those instances of hypotension due to failure of the central neurogenic mechanisms responsible for maintaining peripheral resistance when the blood volume is normal. Under these circumstances, increasing the blood volume farther by large infusions may do harm, particularly if congestive heart failure complicates the picture, and moreover is ineffective as a means of increasing the blood pressure.

Central vasomotor failure apparently is a reversible process in many instances if the blood pressure and circulation to the brain and other vital organs can be maintained long enough for physiologic recovery of the failing mechanisms. Thus a patient with so-called "irreversible shock" may recover if the systemic blood pressure is maintained with a vasopressor agent. This was well demonstrated in patient 32 (A. B.) in whom considerably more blood was replaced than was lost. Yet, due to central vasomotor failure she would have died in shock despite adequate fluid replacement had not her blood pressure been maintained by nor-epinephrine. It took five days before improvement of her vasomotor mechanism was adequate to maintain her blood pressure without the constant support of a peripheral vasoconstricting agent.

Because of its effect in increasing the irritability of the myocardium in the laboratory animal, nor-epinephrine is believed by some to be contraindicated in the treatment of shock secondary to myocardial infarction.[17,24] However, the present studies indicate that disturbances in rhythm occurred in normal patients only when the blood pressure was increased to hypertensive levels. It did not occur when the blood pressure was raised from shock levels to normal, even in patients with infarction. The concurrent use of quinidine and nor-epinephrine is quite feasible and is potentially a method for preventing ventricular ectopic rhythms if this should be of major concern to the therapist. Atropine is effective in preventing the disturbances in auricular rhythm. These observations in the current study suggest that the heart block and the alterations in the origin of the cardiac rhythm have resulted from either direct or reflex effects on the SA or AV nodes; since they are blocked with atropine, they are most likely reflex. In no instance in either the normal or shock patients were there any alterations of the QRS complex, T waves or any disturbances in ventricular rhythm. Since all the patients treated for shock, except the two who failed to have a pressor response, responded adequately to treatment without showing alteration in the electrocardiogram, and in view of the fact that nor-epinephrine has no significant effect on the heart and may actually have a favorable effect on coronary flow,[19] this drug may be considered a valuable adjunct in the treatment of shock secondary to myocardial infarction. However, since all but six of these fourteen patients ultimately died, and since some required larger doses of nor-epinephrine to control blood pressures prior to death, it is apparent that in the absence of adequate myocardial reserve any measures directed solely at maintaining blood pressure are of only temporary benefit.

Raising the blood pressure from shock levels to normotensive levels increases the work load on the heart, of course, but this is necessary to maintain the cerebral and coronary circulation as well as the circulation to less vulnerable vital organs. In order to save further embarrassment to the heart the blood pressure should not be elevated more than the minimal amount necessary to maintain the circulation of blood to these vital organs. One patient in the present study (No. 10, Table II) may well have recovered from his infarction but he died of uremia due to the development of a lower nephron syndrome which resulted from being in shock too long. When nor-epinephrine is administered by con-

tinuous infusion to normal dogs, it causes marked reduction in renal blood flow, renal plasma flow, glomerular filtration rate and maximum tubular transport of glucose.[25] However, when used in shocked dogs in which renal function is markedly depressed, nor-epinephrine infusion actually increases renal function toward control levels.[26] In the present study this was also seen in some of the patients who were anuric because of shock: following injection of the drug there was a significant increase in urine excretion.

In the nine patients with severe infection only three recovered from the shock state and maintained normal blood pressure after nor-epinephrine was discontinued. This again indicated that although shock may be successfully combated by artificial means, the underlying disease process must be corrected before the patient will survive. The shock seen with severe infections is frequently associated with diffuse vascular damage and loss of intravascular fluids through this route. Therefore it is particularly important to maintain adequate fluid administration while administering vasopressor therapy.

As previously stated, most of the patients in the present study were in extremis prior to treatment with nor-epinephrine and in most instances nor-epinephrine was used only after other measures had failed. This is not the best approach to this problem. It is more desirable to use the vasopressor agent as soon as it becomes apparent that its use may become necessary.

All of the cases in the surgical group had a satisfactory vasopressor response to treatment with nor-epinephrine. All of the patients recovered who did not have a fatal complication, such as infection, intravascular hemolysis, pancreatitis, etc. Possibly, if nor-epinephrine had been used earlier there might have been a higher percentage of recovery, even in some of the patients with severe complications. Certainly there is nothing to be gained by continuing to administer fluids and thus increasing blood volume when these are already normal or above and the patient remains in shock due to vasomotor (medullary) failure. Under these circumstances, to continue to administer fluids is only to complicate the picture and probably cause cardiac embarrassment. It is occasionally feasible to use nor-epinephrine in cases of shock resulting from blood loss as a temporary measure for maintaining blood pressure while waiting for blood replacement therapy to be instituted and while corrective surgery is being done. Drops in pressure following anesthesia or medications can often be controlled until the patient is past the critical period.

Care must be exercised in administering nor-epinephrine. Because of the potent vasoconstrictive action of this drug, cutaneous slough is likely to occur following extravasation of the infusing solution or when cut-down procedures are used and the vein ligated. Following ligation of the vein into which the infusion is being administered there is inadequate centripetal flow of blood. This may result in retrograde (centrifugal) flow of the infusing solution which results in intense vasoconstriction of the small vessels and slough. When such cut-down procedures are used, it is advisable to employ small caliber plastic tubing which is threaded up the smaller veins to either the subclavian (arm), femoral (leg), or even up to the inferior vena cava.

TABLE V
SUMMARY OF RESPONSE OF PATIENTS WITH SHOCK TO NOR-EPINEPHRINE

Cause of Shock	No. Patients	No. with Rise of Pressure to Normal	Av. Hours of Treatment Required	Recovery
Cardiogenic	14	12	22	6
Overwhelming infection	9	9	31	3
Medications	6	6	7	6
Postoperative	15	15	33	9
Total	44	42	23	24

The over-all results of all observations on patients in shock are summarized in Table v.

SUMMARY AND CONCLUSIONS

1. Studies were made on twenty-five normal subjects under hospital conditions in order to ascertain the effect of nor-epinephrine on blood pressure, pulse rate, respiration, vital capacity, hematocrit, blood sugar, circulation time and the electrocardiogram. An elevation of the systolic, diastolic and mean blood pressures, together with a decrease in pulse rate was noted in all cases. No significant effect on respiration, vital capacity, circulation time, hematocrit or

blood glucose concentrations was found in the patients receiving subcutaneous nor-epinephrine but the blood glucose was elevated after intravenous nor-epinephrine. Electrocardiographic changes consisting of heart block and supraventricular arrhythmias were noted in three patients when the blood pressure was increased to hypertensive levels. These were apparently reflex in origin since they returned to normal as soon as the blood pressure returned to control levels and they could be arrested by vagal blockade with atropine.

2. Intravenous nor-epinephrine was administered as treatment in forty-four cases of shock not responding to adequate treatment with other measures. A satisfactory and immediate pressor response with maintenance of the blood pressure at desired levels was obtained in all but two patients. This pressor response, the ability to maintain blood pressures at desired levels, the rapid loss of effect after discontinuing nor-epinephrine and the freedom from undesirable side effects make nor-epinephrine a valuable adjunct in the treatment of shock. It is particularly helpful in the patient in whom blood volume is normal or increased, in whom the further administration of intravenous fluids is contraindicated or ineffective. However, the underlying cause of shock, whether it be medical or surgical, must be corrected in order for the patient to recover. Nor-epinephrine should be considered only a temporary means for increasing peripheral vascular resistance and thus maintaining blood pressure. When the use of this drug is contemplated, it should be used as early as possible in order to prevent damage to the brain, kidney, liver and other vital organs. It should not be withheld as a last resort.

3. Fourteen patients with myocardial infarction were treated, all with grave prognosis because of severe shock and other associated complications. Six of the fourteen patients recovered when the blood pressure was adequately maintained with nor-epinephrine. Since most of these patients were already in congestive heart failure, the administration of a significant amount of intravenous fluids was contraindicated. In these circumstances an agent which will increase the blood pressure by peripheral vasoconstriction without concurrent increase in blood volume is particularly helpful. The blood pressure should not be increased above normotensive levels in order to avoid an excessive work load on the heart. Despite the maintenance of blood pressure, if the cardiac function is so poor that cardiac output is excessively depressed, the circulation of blood to vital areas is inadequate and the patient will eventually succumb. There is no evidence to indicate from these studies that nor-epinephrine increases the irritability of the myocardium when the blood pressure is raised from hypotensive to normotensive levels. This is in contrast to raising the blood pressure from normotensive to hypertensive levels.

4. Nor-epinephrine is particularly valuable in severe hypotensive states following the administration of certain drugs to excessively sensitive individuals. This is probably due to the fact that such a response to medication is a peripheral vascular collapse reaction and is of short duration in most instances.

5. Nor-epinephrine is of limited value in the treatment of shock associated with severe infection unless the underlying infection can be rapidly treated with a specific therapeutic agent. If not, the patient dies of his infection.

6. So-called postoperative "irreversible shock" is frequently not irreversible if the blood pressure is maintained long enough for physiologic recovery of the medullary centers provided the underlying cause of the shock is corrected and the patients are given adequate but not excessive amounts of intravenous fluid.

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Non-specificity of the Electrocardiogram Associated with Coronary Artery Disease*

HAROLD D. LEVINE, M.D.

Boston, Massachusetts

ELECTROCARDIOGRAPHERS have found it convenient to conceive of the consequence of myocardial injury in three categories, namely, T wave changes, RS-T segment changes and QRS changes. There is considered to be a gradation in the severity of myocardial impairment from the mildest "ischemic," producing changes in the amplitude and direction of the T wave and in the duration of the Q-T interval, through the more severe stage of "current of injury" which is responsible for RS-T segment shifts, to the most severe damage, actual death of myocardial tissue which, no longer capable of being excited electrically, gives rise to changes in the QRS complex.

It was not until quite recently that the earliest stage of myocardial injury was neatly demonstrated by Bayley, LaDue and York.[1,2] These workers found that the immediate response to tightening a ligature about the descending branch of the left coronary artery of the dog is the development of an inverted T wave or, if originally inverted, of a more deeply inverted T wave, and that prompt release of the ligature is quickly followed by return of the T wave to its original direction or size. They found that retightening the ligature and maintaining the compression for a longer time results, in addition to reappearance of the original T wave inversion, in elevation of the RS-T segment. Prompt release of the tie is again followed by disappearance of the T wave and RS-T segment changes. And they found finally that more prolonged coronary artery compression produces, in addition to the two phenomena just described, a decrease in the magnitude of the R wave and the development of a Q wave, and that, if the ligature is again released promptly, this change is also reversible but that otherwise it is apt to remain a fixed feature of the electrocardiogram.

Only rarely has the opportunity presented itself of observing the initial purely "ischemic" phase of myocardial infarction in man. Generally by the time a patient consults a physician the electrocardiogram has reached at least the stage of RS-T segment deviation. A patient had the very onset of his coronary occlusion while he was being fluoroscoped. He developed, under observation, excruciating chest pain, broke out in a profuse cold sweat and went into a profound state of collapse. A tracing was recorded immediately. It showed a deeply inverted T wave in lead III. Subsequently he showed the characteristic sequential changes of acute posterior myocardial infarction, from which he recovered.

The cascade-shaped or hump-backed T waves that are commonly observed about the "ischemic" margins of acute infarcts, and which may persist for weeks or even months, are more familiar examples of so-called "ischemic" T waves. These generally give rise in time to simply inverted T waves and may have an undistinguished inverted form from the very outset. As a consequence of this many clinicians have developed the habit of referring to inverted T waves, located where T waves should not be inverted, as "ischemic" T waves. Some, in fact, go a step further and, on the basis of this fact of inverted T waves, directly or by inference, make the diagnosis of "coronary artery disease" or "myocardial damage." As is well known, however, changes in the amplitude, direction and duration of the T waves may result from a host of factors, only one of which is myocardial ischemia or anoxia. True, under certain clinical circumstances the most likely explanation may

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be ischemia but then one should be clear that this deduction is made on the basis of *clinical* as well as electrocardiographic considerations. Indeed, it is the purpose of this essay to point out the non-specificity of the electrocardiogram usually associated with coronary artery disease, to illustrate how changes in factors other than coronary artery disease may play a role in producing changes in any or all of the three electrocardiographic phenomena described, to emphasize that these changes represent the effect of *myocardial* rather than *coronary artery* changes, and finally to point out that these myocardial changes may correspond to a *biochemical* as well as to an *anatomical* lesion.

CHANGES IN THE T WAVE

The multiplicity of factors which may influence the T wave of the electrocardiogram is shown in Table I which has been borrowed, in large part, from Bruce Logue. The subclassifications are ours. They are necessarily arbitrary and there is some overlapping. For example, tobacco, which is listed in Group III may apparently in some cases produce its effect through changes in coronary flow and thus properly belong in Group I. Insulin, as another example, may operate through lowering the serum potassium level or through lowering the blood sugar level. It must be remembered that this is a very incomplete listing of the factors known to influence the T wave.

Schwartz and Relman[3] recently described a case in which an electrocardiogram was recorded, for no very good reason, in a constipated young woman with a multiplicity of complaints apparently of supratentorial origin. The tracings showed depressed RS-T segments, inverted T waves, prolonged Q-T interval and U waves, the sort of changes which are interpreted by many electrocardiographers as indicating "coronary artery disease" or "myocardial damage." The changes in this instance were recognized correctly as suggesting potassium depletion.[3] A serum potassium was determined that same

TABLE I
FACTORS AFFECTING THE T WAVE OF THE ELECTROCARDIOGRAM

I. Ischemic or anoxic factors
  1. Coronary arteriosclerosis
  2. Syphilitic ostial disease
  3. Dissecting aneurysm of the aorta
  4. Shock
  5. Anoxemia
  6. Carbon monoxide poisoning
  7. Pulmonary embolism
  8. Anemia

II. Infectious factors
  1. Rheumatic fever
  2. Scarlet fever
  3. Diphtheria
  4. Tonsillitis
  5. Mumps
  6. Measles
  7. Infectious mononucleosis
  8. Rheumatoid arthritis
  9. Trichiniasis
  10. Meningococcemia
  11. Tuberculosis
  12. Sarcoid (?)
  13. Gumma
  14. Myocardial abscess
  15. Hepatic necrosis
  16. Pneumonia
  17. Pericarditis
  18. Scrub typhus

III. Chemical-pharmacologic factors
  1. Digitalis
  2. Quinidine
  3. Procaine amide
  4. Epinephrin
  5. Insulin
  6. Tobacco
  7. Beri-beri
  8. Avitaminosis E
  9. Hypercalcemia
  10. Hypocalcemia
  11. Hypokaliemia (hypopotassemia)
  12. Hyperkaliemia (hyperpotassemia)
  13. Acidosis
  14. Alkalosis
  15. Hyperventilation
  16. Niacin deficiency
  17. Emetine

IV. Nervous or hemodynamic factors
  1. Neurocirculatory asthenia
  2. Tilting
  3. Postural changes
  4. Intracranial disease
  5. Electric shock
  6. Tachycardia
  7. Valsalva experiment
  8. Ice water
  9. Altered vagal or sympathetic tone

V. Endocrine-metabolic factors
  1. Addison's disease
  2. Cushing's disease
  3. Hyperthyroidism
  4. Myxedema
  5. Hemochromatosis
  6. Amyloidosis
  7. Obesity
  8. Sex
  9. Pregnancy

VI. Miscellaneous factors
  1. Tumor
  2. Pericardial effusion
  3. Pleural effusion
  4. Ascites
  5. Post-tachycardia syndrome
  6. Post-extrasystolic T wave changes

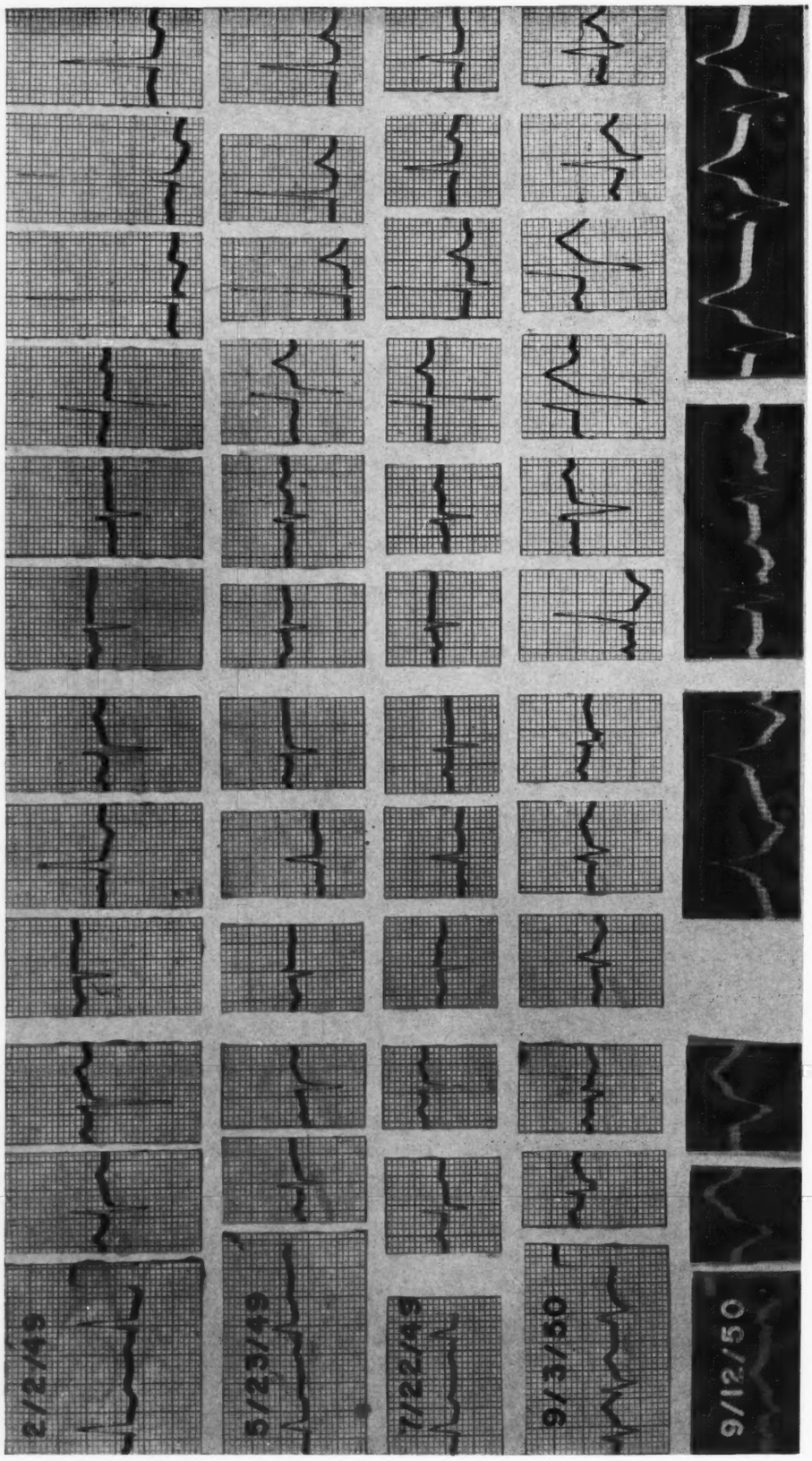

FIG. 1. Instability of the electrocardiogram in left ventricular hypertrophy (potassium changes). Initial set of tracings (2/2/49) characteristic of left ventricular hypertrophy. In the next two sets of tracings the R waves become smaller and the T waves upright and pointed. Tracings of 9/3/50 show right bundle branch block and those of 9/12/50 a greater degree of intraventricular block. Postmortem examination showed left ventricular hypertrophy, no coronary artery disease or myocardial infarction. Here electrolyte changes (potassium intoxication) underlie the lability of the electrocardiogram.

day and was later reported as 1.6 mEq./L., a definitely low reading. When the patient was simply put on a "balance study," she showed a spontaneous potassium retention which coincided with the restoration of a normal serum potassium level and a normal electrocardiogram. It was learned later that this young lady would consider herself constipated unless she had three loose bowel movements daily. To effect this she had been taking large doses of laxatives and had, in the large losses of fluid, developed a pronounced deficit in serum and body potassium.

Another illustration of the non-specificity of changes in the T waves, and one which has interested us for a number of years, is furnished by the instability of the electrocardiogram of hospitalized patients with left ventricular hypertrophy. The prevalent view, it seems, is that the electrocardiogram of left ventricular hypertrophy is a fixed and immutable affair, showing very little if any variation from one recording to another. Indeed a tendency has been observed to attribute instability of the electrocardiogram under such circumstances to the development of certain catastrophic complications, notably acute myocardial infarction. With Dr. Richard Streeper, at the Peter Bent Brigham Hospital, the serial electrocardiograms were reviewed of sixty-two individuals who showed thick left ventricles at autopsy.[4] The initial electrocardiograms of twenty-seven individuals in this group were characteristic of left ventricular hypertrophy, i.e., they showed tall R waves, depressed RS-T segments and inverted T waves over the left ventricle; in this group ten continued to show similar characteristic features while seventeen were unstable. Twenty-nine of the entire group presented original tracings which were abnormal but only *suggested* left ventricular hypertrophy; in this group seven remained unchanged while twenty-two showed unstable tracings. Finally, a third group of six individuals started with perfectly normal curves; only one remained normal while five were unstable. Hence the great majority of these individuals showed changing electrocardiograms. In a given case it was much easier to demonstrate than to explain this instability. In a minority of these cases the changes were associated with increasing or decreasing evidence of congestive heart failure, with pronounced variations in weight, with pulmonary embolism, in a few with the development of bundle branch block and in a considerable number with uremia and concomitant electrolyte changes. In the majority of these cases a multiplicity of factors seemed to operate so that it was difficult to incriminate any one factor. Moreover, even in an individual in whom "spontaneous" changes of this type were observed it was difficult deliberately to bring about similar changes. This aspect of the subject is still under investigation.

An example of the spontaneous variability of the electrocardiogram in left ventricular hypertrophy is shown in Figure 1. The patient was a sixty-one year old man with hypertensive heart disease and uremia. The first set of tracings, recorded on February 2, 1949, was quite characteristic of left ventricular hypertrophy. In the next two sets the R waves were smaller and the T waves were now upright and tent-shaped, suggesting potassium intoxication. Later the patient developed bundle branch block. In this case chemical changes underlie the lability of the electrocardiogram. Figure 2, recorded in fifty year old man with postoperative anuria and hypocalcemic tetany, shows the development of the characteristic appearance of left ventricular hypertrophy coincident with the attainment of a serum sodium level of 160 mEq./L. resulting from the accidental infusion of an excessive amount of sodium.[5] It is not known whether this is a specific electrocardiographic effect of sodium ion, the result of associated fluid retention and of changes in blood volume, or in stroke volume output of the heart. These are only two facets of the many-sided problem of the non-specific T wave.

CHANGES IN THE RS-T SEGMENT

Displacement of the RS-T segment is generally held to be synonymous with a "current of injury." When this phenomenon changes rapidly over a period of several days, the inference of myocardial injury is quite definite; and although this phenomenon furnishes stronger evidence of muscle damage than mere T wave changes, RS-T segment changes may likewise result from other causes. The RS-T segment may be depressed in potassium intoxication, or in the opposite extreme, namely, potassium depletion, as mentioned previously. An auricular T wave may at times deform the RS-T segment. The process of auricular repolarization generally coincides in time with ventricular depolarization; the auricular T wave is there-

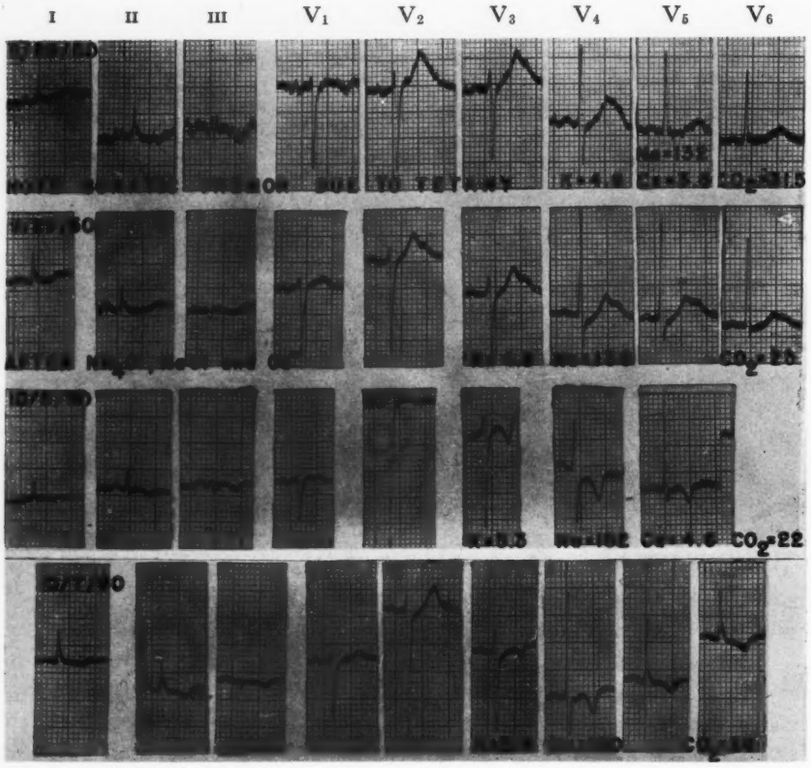

FIG. 2. Instability of the electrocardiogram in left ventricular hypertrophy (calcium and sodium changes). Patient with chronic pyelonephritis and hypertensive heart disease. The T waves become inverted and the Q-T interval shorter as hypernatremia is substituted for hypocalcemia. Serum potassium levels were normal throughout.

fore obscured in the QRS complex. I recall a patient with mitral stenosis with regular sinus rhythm who was to have a mitral valvuloplasty. Preoperatively his electrocardiograms showed a normal P-R interval and the usual broad notched P waves that are so characteristic of mitral disease. During the period of anesthesia induction the anesthetist, alerted to the dangers of subendocardial ischemia, was alarmed when he noted a profound depression of the RS-T segment. Examination showed that what actually had happened was that the P-R interval had, for some reason, become shortened, thus delaying the time of inscription of the auricular T wave beyond the QRS complex and producing a depression of the RS-T segment. The anesthesia and the operation proceeded satisfactorily without the development of myocardial necrosis. Incidentally, there is very suggestive evidence that cortisone quite regularly shortens the P-R interval.[6] It may well be that this is a distinctive electrocardiographic feature of the so-called "alarm reaction."

Not infrequently slight deviations of the RS-T segment, amounting to a millimeter or so, may be observed in one or more leads as a perfectly normal variation. The T wave is upright and there are no abnormalities in the QRS complex. Repeated tracings show that this is a fixed change. When the RS-T segment is elevated even the experienced observer may find it difficult from a single tracing to state whether or not this represents the incipiency of acute myocardial infarction or pericarditis. Under suspicious circumstances it seems fair to say more attention would be paid to this change as possibly pathologic. Although this deviation is apt to be most pronounced in the precordial leads, it may have a more general distribution. Nitroglycerin may at times cause this elevation to disappear or become less pronounced; it is difficult to say whether this represents the subsidence of ischemia or is the direct result of cardiac acceleration produced by nitroglycerin. It seems rather doubtful that this change represents a current of injury set up with each heart beat on contact of the heart with the chest wall; by analogy with "touch" currents of injury

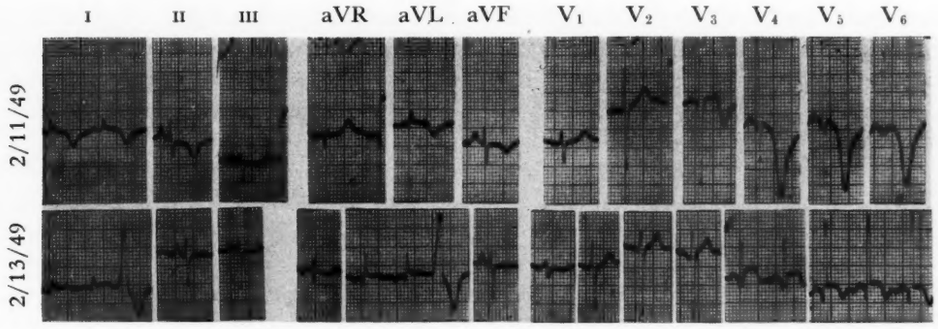

FIG. 3. "Ischemic" T waves and "currents of injury" in intracranial disease. The initial tracings show deeply inverted T waves resembling those seen in Bayley's dogs. The second set, recorded two days later, shows RS-T segment elevation and less deeply inverted T waves, a sequence of changes very suggestive of myocardial infarction. Postmortem examination showed ruptured aneurysm of the circle of Willis; no myocardial or coronary artery disease.

induced by contact of an intracardiac catheter with the endocardium one would expect such a contact to produce T wave inversion as well as RS-T segment elevation. The explanation that this phenomenon is due to initiation of the process of repolarization in some parts of the vigorously beating heart before depolarization is completed in other parts of the heart is merely to restate, not to clarify, the fact. It seems proper to consider this an unexplained phenomenon.

Changes in the RS-T segment, as well as in the T wave, may also develop for reasons not entirely clear at the present time, in association with disease of the central nervous system. Figure 3 was recorded in a sixty-nine year old woman who was admitted and remained in coma. The first strip shows cascading T waves very much like those seen in Bayley's dogs with ligatures about their descending coronary arteries. Later, as these T wave changes waned, the RS-T segments became elevated. The diagnosis of myocardial infarction was made. Postmortem examination showed a ruptured aneurysm of the circle of Willis but on meticulous microscopic examination no evidence of myocardial infarction or of pericarditis. Dr. George Burch tells me that he has seen a number of similar cases of intracranial disease associated with abnormal electrocardiograms of this sort.[7]

The exact mechanism of these electrocardiographic manifestations of disease in the central nervous system is poorly understood. Beattie, Brow and Long[8] found that stimulation of the basal ganglia produces numerous arrhythmias. Dikshit[9] found that the injection of caffeine into the cerebral ventricles of cats produced ventricular premature beats and, much more relevant to the present discussion, that during the period when extrasystoles were frequent the regular beats showed depressed RS-T segments and inverted T waves; after sodium barbitone the heart showed fewer irregularities and the T waves of the regular beats became flat or upright. Abnormalities have been recorded in the T wave in association with neurocirculatory asthenia. These are often held to indicate dysfunction in the sympathetic or parasympathetic divisions of the autonomic nervous system. The criteria upon which these distinctions are made has never been clear to me and the validity of such deductions has recently been criticized.[10] I have had no direct experimental experience with nervous effects bearing upon the *ventricular* T wave but, in a study of displacement of the cardiac pacemaker carried out in human subjects with an intracardiac electrode, it was possible to present suggestive evidence that, under certain circumstances, vagal stimulation in addition to displacing the cardiac pacemaker may alter the speed of the repolarization process in the auricle.[11] This corresponds to similar observations by Cohn and MacLeod in the experimental animal.[12]

When confronted with a clinical situation typical of acute myocardial infarction associated with QRS, RS-T segment and T wave changes in the electrocardiogram, the tendency is to make an unequivocal diagnosis of acute myocardial infarction. Generally this conclusion will be justified by the subsequent course of events but even here it would seem wise to hold the mental reservation that to deserve this interpretation these changes must be dynamic

rather than static. To be specific, the RS-T segment changes associated with acute myocardial infarction are characteristically transitory; they are apt to vanish in a few days or a week. Rosenbaum, Johnston and Alzamora described a case in which these RS-T segments remained displaced from the isoelectric line.[13] At autopsy not myocardial infarction but a large tumor metastasis was found in the heart. This change is attributable to a constant current of injury due to a difference of potential between myocardial tissue capable of responding to the activating impulse and tumor tissue not so capable. Since the early observations of R. Langendorf[14] and J. D. Cameron[14] and later those of Rosenbaum et al.[13] similar constant RS-T segment deviations have also been observed frequently as a clue to ventricular aneurysm. The reason for this peculiar electrocardiographic finding is not yet established. The explanation which accords most closely with the observed facts is that of Gordon Myers[15] who contends that the changes are due to the relationship of the exploring electrode, through the electrical "window" formed by the old infarct, with the endocardial aspect of the current activating the opposite hypertrophied left ventricular wall. The possibilities remain, however, that the changes are related to a "current of injury" at the margins of the old infarct generated repetitively with each successive heart beat or perhaps to the combined effect of the transmural non-excitable window and a chronic pericarditis.

CHANGES IN THE QRS COMPLEX

We have seen that changes in the T wave *frequently*, while changes in the RS-T segment *occasionally*, result from other causes than myocardial ischemia or injury. The development of a "significant" (i.e., a broad and prominent) Q wave, and thus of the projection of so-called cavity potentials to areas where epicardial potentials are expected is, in the vast majority of instances, the result of myocardial infarction, and this in turn is generally contingent upon disease of the coronary arteries. At times, however, this type of change can be effected by factors other than myocardial infarction.

By and large, whereas RS-T segment and T wave alterations are transitory or may be transitory, changes in the QRS complex are generally permanent. To be sure, there are rare instances of undoubted myocardial infarction in which a Q wave may be present for a day or two only to disappear subsequently. This phenomenon has never been satisfactorily explained.

Furthermore, although the development of broad, prominent Q waves usually corresponds to myocardial infarction, there are a few exceptions to this generalization. Fibrotic replacement of myocardial tissue, however produced, can lead to the transmission of "cavity potentials" to the surface of the heart. Figure 4A shows the electrocardiogram recorded in a case of scleroderma.[16] The R waves were absent or very small in leads V_1 to V_4, a finding generally associated with old anteroseptal infarction. At autopsy in this case the myocardium (Fig. 4B and C), particularly in the anteroseptal region, showed extensive replacement with fibrous connective tissue. Although theoretically this change should be transmural or subendocardial in distribution to be capable of producing QS complexes in the one case or QR complexes in the other, this did not necessarily correspond to the histologic facts in the few cases I have studied. Similarly I have observed characteristic evidence of old myocardial infarction in individuals in whom extensive study, including the findings at surgery, established the presence of chronic constrictive pericarditis without coronary artery disease. In these cases the electrocardiographer was apt to mislead the clinician. It seems likely that this finding is somehow related to the intramyocardial extension of fibrous connective tissue from the pericardial scar.

It is clear further that these changes may be induced by processes in the myocardium other than fibrosis, namely, by any disease which converts the healthy myocardium into tissue which is no longer capable of responding to the activating impulse. Thus amyloidosis of the heart[17] and, as we have already seen, tumor metastasis to the heart have been reported as bringing about similar changes. The electrocardiogram in the case of cardiac amyloidosis described by Wessler and Freedberg showed absent R waves in leads V_1 to V_3, interpreted as compatible with an old myocardial infarct. At postmortem examination injection-dissection showed intact coronary arteries; histologically there was extensive amyloid replacement of the myocardium but no myocardial fibrosis.

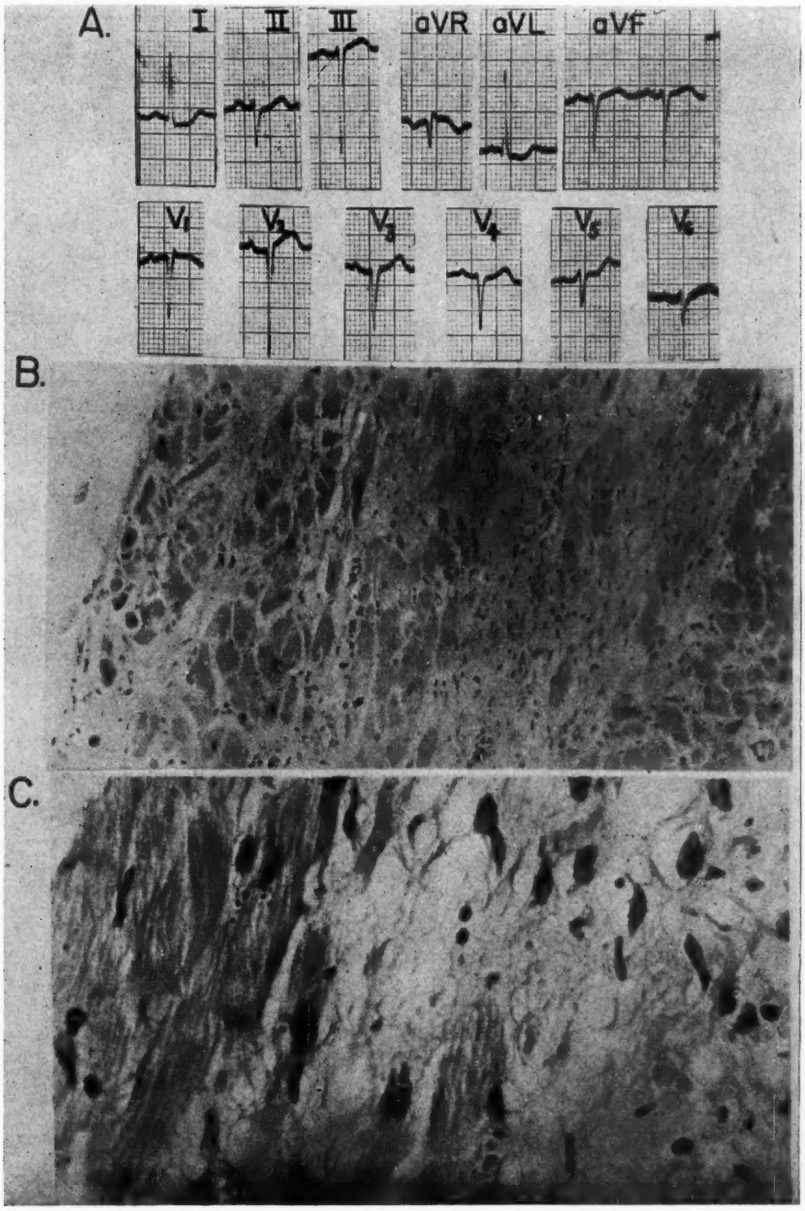

FIG. 4. "Cavity potentials" transmitted through myocardium overgrown by sclerodermatous changes. A, small R waves in leads V_1 to V_4, very suggestive of old anteroseptal myocardial infarct; B, low power photomicrograph showing extensive myocardial fibrosis; C, high power detail of same; no coronary artery disease.

The point of all this is, of course, that, in a sense, our title is a misnomer. The electrocardiogram reveals, not changes in the coronary arteries but changes in heart muscle. Although, by and large, the myocardial changes reflect disease of the coronary arteries they can, in certain instances, be independent of coronary artery disease and the result rather of other diseases of the myocardium.

STRESS TESTS FOR CORONARY INSUFFICIENCY

There are a number of patients in whom careful history, physical examination and various routine laboratory procedures leave one in considerable doubt as to the existence of angina pectoris. In these puzzling cases the employment of one of the so-called stress tests may reward the clinician with evidence for coronary in-

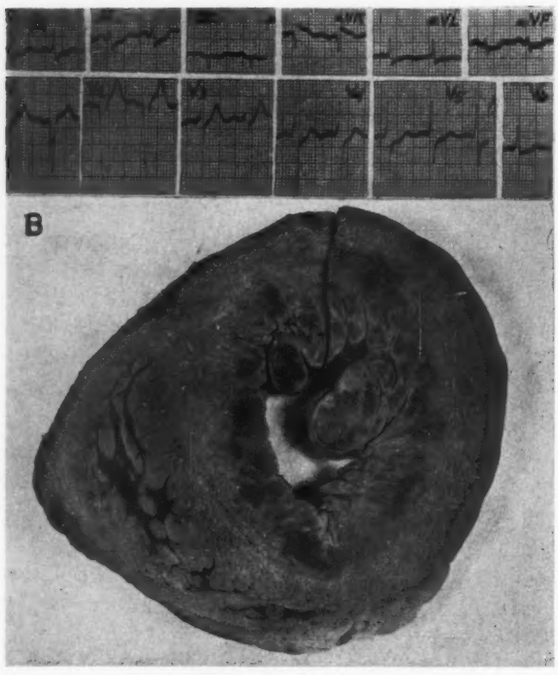

FIG. 5. Subendocardial infarction; A, tracings showing depressed RS-T segments similar to those developing in spontaneous or induced angina pectoris; B, transverse section of heart from same patient showing ring-like infarct surrounding left ventricle.

sufficiency. Those who conceive of angina pectoris as the effect of spasm of the larger coronary arteries would, in spontaneous or induced coronary insufficiency in man, expect to find electrocardiograms resembling those recorded in Bayley's dogs described at the beginning of this lecture. Although in rare instances such changes have been recorded, generally these tests demonstrate electrocardiographic alterations which we have come to associate with transitory subendocardial ischemia. Figure 5A shows the electrocardiogram of a patient with calcific aortic stenosis during an attack of severe chest pain and collapse. It shows depressed RS-T segments in leads I, II, aVF and V_4–V_6, quite like those seen in a "positive" Master two-step test. Postmortem examination showed a ring-like subendocardial infarct. (Fig. 5B.) It seems probable that these changes represent an exaggeration of the normally prolonged duration of the excited state in the subendocardial laminae of the ventricle due to an inadequacy of the blood flow to these inner layers of the heart, whether as the result of accentuation of the normal gradient in pressure between the inner and outer layers of the ventricle or due to actual spasm of the deep penetrating coronary branches.

It is not always easy to interpret a two-step or anoxemia test. Mere changes in heart rate can bring about changes in the ventricular gradient of a normal heart with depression of the RS-T segment and/or inversion of the T wave. It requires considerable experience or a better skill in the measurement of the gradient than most of us possess to be able to evaluate minor changes. Consequently one is frequently forced to report the test as inconclusive or doubtful.

Digitalis therapy is said also to produce "false positive" exercise tests. From the gross resemblance of the tracings of "subendocardial ischemia" with those resulting from the effect of digitalis this comes as no great surprise. Digitalis in toxic doses is, moreover, capable of producing focal myocardial lesions in the papillary muscles, in the left ventricular wall and in the interventricular septum, perhaps more extensive subendocardially.[18–21] The specificity of these changes has not been proved since similar lesions may result from toxic doses of pitressin,[22] prolonged oxygen deprivation[23] or potassium depletion.[24–27]

SOME LIMITATIONS IN THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF MYOCARDIAL INFARCTION

Although a recent study concerning the accuracy of routine electrocardiography showed a high degree of precision in the diagnosis of *acute* myocardial infarction, it left much to be desired in the electrocardiographic detection of *old* infarcts. *Multiple* infarcts were notably missed electrocardiographically. The limitations of the electrocardiographic method may be explained by: (1) small size of infarcts, (2) their location in "non-strategic" areas, (3) in the case of multiple infarcts the electrical dominance of one infarct over another, (4) changes in the deeper laminae cancelling oppositely directed changes in the superficial laminae of the ventricle and (5) non-projection of currents of injury of limited distribution to any of the twelve leads in current use. (Fig. 6.) Very often the reason for the failure of the technic is not clear.

At present interest centers upon the vectorcardiogram as a substitute for and as possibly superior to the electrocardiogram in the detection of myocardial infarction. It has been known for some time that it is possible to translate from

two simultaneously recorded conventional limb leads a record of the moment-to-moment electrical activation of the heart. A line connecting the series of instantaneously recorded vectors thus inscribed is called a vectorcardiogram. Wilson, using an oscilloscopic set-up, showed how it is possible to record this frontal plane vectorcardiogram directly. He suggested that this technic might be useful as a teaching aid and as a tool in cardiac diagnosis and research. More recently attempts have been made to reconstruct this loop as it lies in the three-dimensional thorax by the use of the oscilloscope. Thus far there has been some difference of opinion as to the proper way to record such a spatial loop. Burch and his group have used a tetrahedral frame of reference whereas Grishman and Scherlis prefer a cubic reference system. It is claimed that study of the loops recorded either way is more informative than the so-called scalar electrocardiogram currently in use, and that the latter is a derivative of and can be predicted from the former. The electrocardiogram comprises, as it were, a set of views of a rocket in flight, namely, the projection of the action current of the heart as photographed from a series of vantage points on the surface of the body. By contrast the vectorcardiogram may be conceived of as a record made by riding along on the tail of this rocket. There are certain distortions in the electrocardiogram, certainly in the chest leads, due to the fact that the exploring electrodes are not truly remote. There are probably similar distortions, although perhaps not so pronounced, in the vectorcardiogram recorded by either the tetrahedral or cubic method. It is understandable, therefore, that changes in certain instances may be found by one method and not by the other. Furthermore, direct comparison of one with the other may not, strictly speaking, be valid because each may not be recorded in the same phase of respiration. Since there is as yet no court of final appeal it may be futile at the present stage of our knowledge to compare the result of one technic with that of another. Until some one produces a convincing method of recording a "true" vectorcardiogram or until we have had more experience with present methods, preferably with postmortem correlations, the relative merits of the vectorcardiographic versus the electrocardiographic method should be regarded as still undetermined.

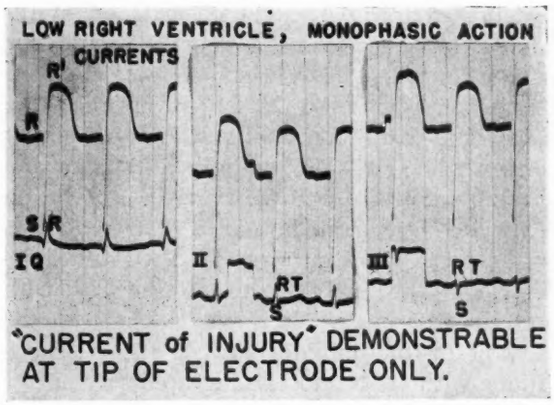

FIG. 6. Locally produced currents of injury not detected in electrocardiogram. Upper curves show intracardiac electrograms recorded in the right ventricle. The catheter tip here has the two-fold function of producing and recording a "current of injury" (monophasic action current). Simultaneously recorded conventional limb leads (lower curves) show no concomitant RS-T segment displacements. Unipolar limb and chest leads similarly failed to detect accompanying RS-T shifts.

Let us now consider the theory underlying the diagnosis of myocardial infarction by means of the vectorcardiograph. The contribution of each part of the heart muscle to the vectorcardiogram is dependent upon the muscle being intact and therefore capable of responding to the activating impulse. Each segment of the ventricular muscle contributes its share to the rounding out or salience of the loop. If a part of the heart muscle is damaged, its electrical output is decreased, the total balance of electrical forces is disturbed and the appearance of the loop is distorted. This may result in malposed, flat, concave or clover-leaf shaped loops. It seems possible that study of the vectorcardiogram may help solve the frequently vexing problem of the differentiation of posterior myocardial infarct from a normal horizontal heart.

Likewise the differentiation between acute cor pulmonale and acute posterior myocardial infarction is not always an easy matter. Either condition can produce S waves in lead I, Q waves in lead III and depressed RS-T segments in the precordial leads. The detection of a significant Q wave in lead aVF is said to argue in favor of a posterior myocardial infarct but this is not always a reliable sign. The differentiation is rendered more difficult by the possible co-existence of the two conditions, myocardial infarction not infrequently being complicated by pulmonary embolism and, in rare instances, pulmonary embolism being complicated by the

development of myocardial ischemia or infarction. Helpful evidence in favor of acute cor pulmonale may be a shift of the so-called "transitional zone" to the left, inversion of the T waves over the precordium, the development of incomplete right bundle branch block or of a pronounced sinus tachycardia, while elevation of the RS-T segment in lead aVF or lead III, or the presence of tall upright T waves in the chest leads, are more apt to be associated with posterior infarction. We await with interest the attempt to differentiate between the two conditions with the vectorcardiographic technic.

It is not the purpose of this presentation to paralyze the physician or to stifle his diagnostic courage with overemphasis on the shortcomings of electrocardiography. A clinical diagnosis may be justified in the absence of all confirmatory laboratory evidence. The clinician should be clear in his own mind, however, precisely upon what considerations his judgment is based.

SUMMARY

Changes in the T wave, in the RS-T segment, and in the QRS complex of the electrocardiogram generally reflect, respectively, myocardial ischemia, current of injury or death of muscle. The T wave, the most labile and least specific feature of the electrocardiogram, may be affected by a great variety of factors, only one of which is ischemia. Changes in the RS-T segment usually but not always correspond to acute muscle damage. It is generally transitory, rarely permanent. Like the T wave this may indicate an anatomical or a biochemical lesion. QRS changes practically always signify death or replacement of heart muscle; this is generally associated with coronary artery disease. Rarely it may result from heart muscle damage from other causes.

The electrocardiogram is quite accurate in the detection of acute myocardial infarction but inaccurate in the diagnosis of old or of multiple infarcts. It remains to be seen whether the newer vectorcardiography will attain a greater accuracy.

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Review

Bronchomotor Tone*

A Neglected Factor in the Regulation of the Pulmonary Circulation

SIMON RODBARD, M.D.
Chicago, Illinois

An adequate understanding of the control of the pulmonary circulation has long lain hidden behind the curtain of the bony thorax. From the voluminous data provided by anatomists, physiologists and clinicians, two generalizations concerning the regulation of the lesser circulation have developed. These are in direct contradiction to each other. Each has been a valuable guide to research but both fail to explain certain established facts.

ARTERIOLAR TONE CONCEPT

One school of physiologists[1,2] and clinicians[3–8] tends to regard the pulmonary vessels as essentially similar to those in the systemic circulation, with vasomotion regulating the pulmonary arterial pressure and blood flow. This interpretation is based on data which show that the pulmonary arterial pressure may be affected acutely in a variety of conditions, as for example in hypoxia,[2,6–8] and with the administration of 'pulmonary vasoactive" drugs.[4,5] The heightened pulmonary arterial pressure seen in mitral stenosis and left heart failure is also ascribed, at least in part, to constriction of the pulmonary arterioles.

In the systemic circuit vasomotion operates to distribute the cardiac output to organs having variegated functions and varying needs for blood supply. It is generally accepted that each part of the lungs has the same general function as any other part. The shunting of blood through various pulmonary segments by arteriolar contriction therefore can have no normal functional value comparable to that achieved in the systemic circulation. Localized arteriolar constriction would reduce flow through a portion of the lung but probably would have little effect on the total pulmonary resistance.

It is often implied that a generalized rise in pulmonary arteriolar resistance helps to protect the lungs against the development of pulmonary edema. Such a generalized constriction in the pulmonary arterioles would throw an added burden on the right heart, but could not reduce the flow of blood to the lungs without producing hypoxia, and thereby bringing on a deleterious train of events. Pulmonary hypertension would thus serve no known function but would represent a disorder parallel to systemic hypertension.[4]

The weak and contradictory responses of the pulmonary blood vessels to nerve stimulation and to the administration of drugs[9] provides no balm for this school of active pulmonary regulation. The delayed response of the pulmonary artery pressure to drugs has suggested that these changes are merely secondary to a primary action on the systemic vessels.[9,10]

The very existence of significant quantities of smooth muscle in the pulmonary arterioles has been challenged. Careful work of anatomists[11,12] and pathologists[13–15] has shown that in man the normal pulmonary arterioles consist of wide tubes of endothelium surrounded by a single layer of elastic fibrils. It seems improbable that such vessels could control the pulmonary circulation by their active contraction.[13] In some species, such as the rabbit, the pulmonary arterial musculature is well developed[12,15] but this condition does not prevail in normal man. The occasional muscular development seen in the pulmonary arteriolar wall of man is associated with pulmonary hypertension. Available evidence shows this to be a secondary effect

* From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill. Aided by grants from the National Heart Institute (H-690), the J. N. and A. D. Nast Fund for Cardiovascular Research, and the Michael Reese Research Foundation.

following upon the increased tension, and not a primary mechanism serving to raise the arteriolar resistance.[16]

PASSIVITY CONCEPT

A second school, considering the weak and equivocal responses of the pulmonary circulation to nerve stimulation and to the exhibition of potent cardiovascular drugs, holds that the lungs are essentially sponge-like structures passively accepting the right ventricular output; the blood flows passively downhill through the pulmonary vascular bed to the lower pressure level of the left auricle.[9,17] Vasomotor activity of the pulmonary arterioles is held to be a "feeble vestigial mechanism without important function."[9,17] The failure of vasoactive drugs to affect the pulmonary arterial pressure on first passage through the pulmonary arterioles is cited as support for this concept.[9,17] The residual volume of blood in the lungs is considered a simple function of the difference in the pumping action of the two ventricles. Pulmonary engorgement followed by pulmonary edema therefore becomes an inevitable consequence whenever the output of the left ventricle fails to equal that of the right ventricle.

The passivity concept has led to many dilemmas. For example, the pulmonary arterial pressure is known to be high (30 to 80 mm Hg, mean) in many compensated patients with mitral valvular[18,19] and congenital heart disease[3,6,10,19] and in chronic cor pulmonale.[3–] Under these circumstances pulmonary edema ought rightly to be present unless some mechanism is available to prevent the transfer of this elevated pressure to the lung capillaries, or to prevent transudation of fluid across the capillary wall into the alveolus.

EXTRAVASCULAR REGULATION CONCEPT

The foregoing contradictions led us to undertake an analysis of the comparative anatomy and physiology of the pulmonary circulation[20,21] in an attempt to elucidate the mechanisms regulating flow of blood through the lungs. Our studies have resulted in the development of a working concept[22] which has proved of value in guiding the experimental approach to the problem, and in interpreting much of the experimental and clinical data in the literature. This concept suggests that much of the regulation of the pulmonary blood pressure and blood flow depends upon mechanisms extrinsic to its blood vessels. It accepts as a fundamental thesis that the control of the blood flow through the lungs is intimately associated with the respiratory function. The mechanism of this extravascular regulation is believed to operate via bronchiolar tone. Contraction of the bronchioles produces air entrapment in the alveoli. The increased air pressure compresses the pulmonary capillaries and inhibits transudation across the capillary wall in a manner similar to that produced by extrinsic positive pressure apparatus. An increase in bronchotonus can in this way counteract pulmonary congestion and edema. When marked, such an increased bronchotonus may contribute significantly to pulmonary hypertension and its sequelae. The exact extent of this extravascular pulmonary regulation remains to be determined; however, a consideration of the data to be presented would make it appear that these mechanisms play a significant role which deserves further attention. A brief review of some anatomic and physiologic cardiopulmonary relationships will help to provide a basis for the consideration of this mechanism.

BASIC CONSIDERATIONS OF THE PULMONARY ANATOMY AND PHYSIOLOGY

To facilitate gaseous exchange, blood passing through respiratory organs must be separated from the environmental gases by the thinnest possible membrane.* The ultra-thin pulmonary capillaries virtually hang in the alveolar space,[11,12] providing a maximal exposure of the contained blood to the environmental gases.

The requirement of a gossamer capillary wall, unsupported by any tissue pressure, places an apparent limitation on the respiratory circulation: the need for a low capillary pressure. Whenever the pulmonary capillary pressure rises above the osmotic pull of the plasma proteins, fluid will transude across the vessel wall. Under these circumstances the pulmonary capillary would soon simulate the renal glomeru-

* The long controversy over the existence of an epithelium over the pulmonary capillaries finally appears settled in the affirmative. This epithelium, so thin that its visualization is accomplished only at the limit of the resolving power of the light microscope, has been brought into clear view with the electron microscope. Even with this new technic the epithelium frequently thins out over the capillaries so as to become almost indistinguishable at high electron magnification. The thickness of the epithelial layer ranges from 0.1μ to 0.7μ or even more. The epithelial nuclei appear especially where the alveolar walls are relatively thick. (Low, F. N. Electron microscopy of the rat lung. *Anat. Record*, 113: 437–443, 1952.)

lus with formation of a filtrate. This fluid coating the capillary wall would increase the effective barrier to gas exchange, reduce oxygenation and place life in jeopardy.

The great distensibility of the unsupported capillaries and the enormity of the pulmonary capillary bed operate together to reduce resistance to flow through them to a minimum. The resistance to flow through the pulmonary arteries and arterioles also is very low. The normal pulmonary arterioles are wide tubes which normally have an extremely limited, if any, capacity for vasomotion.[11–14] The pulmonary arteries are spacious, multibranched channels capable of handling many times the resting cardiac output with little resistance.[11] This superfluity of wide conduits is emphasized by the fact that moderate exercise in man, with a several-fold increase in the cardiac output, may result in no significant rise in pulmonary arterial pressure.[23] Even the systemic venous pressure can be made to cause perfusion of the lungs, with little aid from the right ventricle.[24]

These basic requirements demanded for all respiratory organs has resulted in the striking fact that the normal pulmonary arterial pressure is about 25/10 mm. Hg, with a mean of about 15 mm. Hg, in a wide variety of species of animals,[20] including birds, amphibia, reptiles and mammals such as the dog, cat, rat and man.

The pulmonary capillaries are brought into contact with the air of the outside world through the medium of the pulmonary airways. The behavior of these tubes plays an important role in the pressure relationships operating on these vessels.

The attention of anatomists has been generally focused on those parts of the lung playing an obvious role in respiratory function, such as the blood vessels, alveoli and the general structure of the air passages. Others, interested in the parenchyma, have remarked that from a structural point of view the lung may be considered to be essentially a *muscular* organ.[11,25] This muscle is found outside the vascular tree, in the walls of the bronchi and the bronchioles. The ubiquity and luxuriance of this muscular structure has been generally ignored by many physiologists and clinicians interested in cardiopulmonary relationships.

The pulmonary musculature is richly innervated by vagal and sympathetic pathways. By contrast with this rich innervation of the bronchiolar musculature, the evidence for innervation of the pulmonary blood vessels in man is scanty.[12,26,27] Pressure sensitive muscle spindles of the type found in the carotid sinus are present in large numbers in the bronchiolar musculature.[12,26,27] As with other enterogenic organs, the vagal fibers usually provide for an increase in muscular tone, while sympathetic fibers provide relaxation. Changes in bronchomuscular tone have been demonstrated in a wide variety of conditions and can be produced uniformly by such agents as histamine, acetylcholine and adrenaline. It is through these bronchial pathways that we believe the pulmonary circulation to be indirectly regulated to a significant extent.

To date, no certain physiologic function has been ascribed to the pulmonary muscles. They probably play a role in normal respiration,[25,28–32] and they may operate to help regulate the pulmonary circulation as suggested below. The only generally recognized role of the rich bronchiolar musculature is in the production of asthma. It is, of course, unlikely that the primary role of such a widespread muscular system would be the production of disease.

From an evolutionary point of view, the bronchiolar muscle of the lung may be considered to have the task of preserving its respiratory function, i.e., to keep the lung dry. From lungfish to man the laryngeal muscles operate to keep water from entering the lung.[28] The other muscles of the lungs may be viewed as subserving the same function. Constriction of the bronchioles during the act of coughing[30,31] acts to increase the velocity of the out-going air and thus assists in clearing the pulmonary passages of collections of mucus and foreign materials. The bronchiolar musculature apparently may also have a similar "dehydrating" function in preventing the transudation of fluid into the alveolar spaces.

Direct bronchoscopic and fluoroscopic observations have firmly established that the airways dilate and elongate during inspiration, and narrow and shorten on expiration. It has been generally held that these effects are passive but more recent evidence indicates that the bronchioles can respond reflexly with sudden changes in tone.[33,34] The changes in cross-sectional area of the bronchi and bronchioles are quite remarkable, the tubes during inspiration acquiring as much as eight times their area during expiration.[31] Constriction of the airways during expiration, whether passive or active, would increase the resistance to egress of air from the

peripheral bronchial tree. In this way it would play a role in the regulation of intra-alveolar pressure and of the pulmonary circulation.

During normal inspiration filling of the pulmonary vessels is facilitated by the increased venous return to the right heart.[35–39] The reduced intra-alveolar pressure of inspiration permits optimal filling of the pulmonary capillaries, with a consequent rise in intrathoracic blood volume. (Fig. 1.) The increased alveolar pressure of expiration may act as a physiologic positive pressure mechanism, compressing the pulmonary capillaries and reducing their size. (Fig. 1.) The positive pressure effect of expiration may also force accumulated alveolar transudates back through the capillary wall and reduce the blood reservoir of the pulmonary system during this phase.

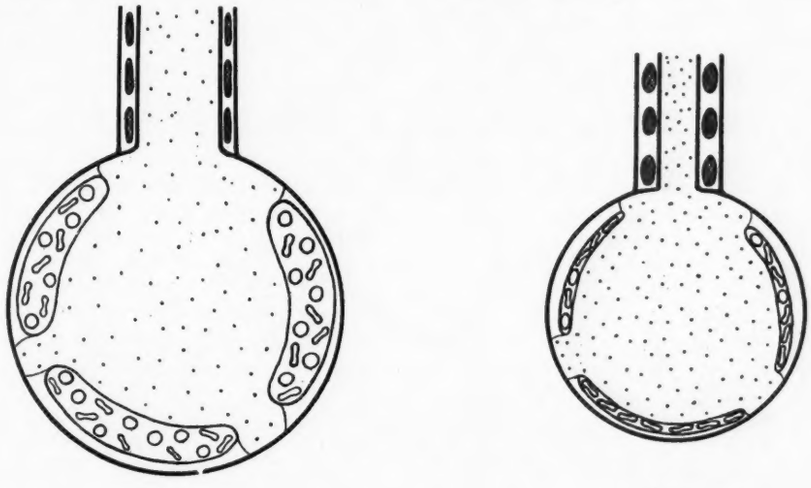

FIG. 1. Schema to illustrate the effect of respiration on the pulmonary circulation. The alveolus in inspiration is shown with large volume. Its contained air is indicated by the widely separated dots representing relative rarefaction due to the diminished intra-alveolar pressure. The bronchiole is widely dilated, permitting free access of air into the alveolar chamber. The reduced intra-alveolar pressure permits engorgement of the pulmonary capillaries shown filled with red blood cells. The alveolus in expiration is smaller due to the diminished air volume. The bronchiole is constricted, increasing the resistance to outflow of air. The increased air pressure in the alveolus (suggested by the greater concentration of dots) acts to compress the capillaries and thus increases the resistance to flow through these vessels.

MEASURES OF INTRA-ALVEOLAR PRESSURE

The importance of the intra-alveolar pressure as already outlined could be satisfactorily assayed if some adequate measure of its level in various conditions were available. Unfortunately no acceptable direct method has been developed. The alveoli are so minute and so fragile that attempts at direct measurements probably would introduce serious artefacts. An approach to the state of the intra-alveolar tension may be obtained by determination of the pressure outside the alveoli, i.e., the intrapleural pressure, or by analysis of the pulmonary arterial pressure curve.

Intrapleural Pressure. If the chest is opened the normal lung will collapse, with the visceral pleural wall moving rapidly away from the parietal pleural wall. Under normal circumstances, with the chest closed, this collapsing tendency may be measured as the intrapleural pressure. The ability of the normal lungs to follow the movements of the chest wall has led to statements that the "elasticity" of the healthy lung is "perfect," i.e., the intrapulmonary pressure changes little during the respiratory changes in lung volume.[40] However, if the airways are partially obstructed because of heightened bronchomotor tone, or mucosal edema, inflammation or secretion, the intrapleural pressure may be markedly affected during respiration. In such cases entrapment of air in the alveoli will produce a relatively "rigid" lung, especially during expiration. These effects can be seen acutely in the heightened respiratory fluctuations in intrapleural pressure follow-

ing bronchoconstriction, as in the administration of histamine or during an attack of asthma.[41] Similar fluctuations in pressure during respiration will occur when congestion or parenchymal disease of the lungs alters its "elastic" qualities. Whenever parenchymal change can be excluded, the magnitude of the change of intrapleural pressure for a given depth and velocity of respiration can be considered an index of the bronchomotor tone.[41,42]

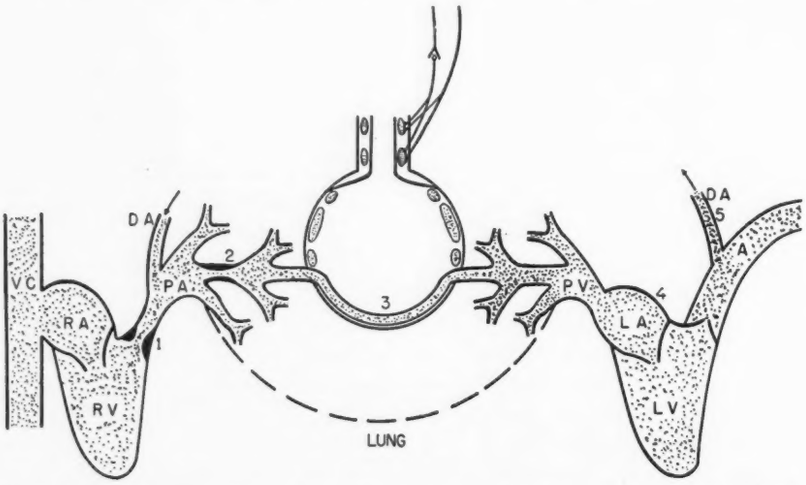

FIG. 2. Schema illustrating sites of increased resistance to the flow of blood through the pulmonary circulation. The return from the vena cavae (VC) passes through the right auricle (RA) into the right ventricle (RV). Resistance to outflow from the ventricle can occur in the region of the pulmonary valve in the form of a valvular or infundibular stenosis (1). The blood then flows into the pulmonary artery (PA) and may meet a resistance in the arteriolar tree due to organic changes in these vessels (2). In the alveolar capillaries the resistance to flow (3) may be augmented by an increased intra-alveolar pressure, as suggested in Figure 1 (for example, by an increase in bronchomotor tone brought on by change in nerve tone as shown in diagram). Beyond the alveolus, resistance (4) may be encountered in a heightened pressure in the left atrium (LA) secondary to abnormal function of the mitral valve or left ventricle. An increased load on the pulmonary circulation may also be produced by congenital defects (5). These are suggested in this instance by the ductus arteriosus (DA) arising from the aorta (A) at the right and inserting into the pulmonary artery (PA) at the left.

Pulmonary Arterial Pressure. The normal low resistance to flow through the pulmonary arteries and arterioles and their limited capacity for vasomotion have already been pointed out. Any acute rise in pulmonary arterial pressure must therefore come from a resistance beyond the arterial tree, e.g., at the capillaries or beyond them. The capillaries normally consist of a thin endothelial wall without muscular or significant connective tissue support. Rouget cells and other constrictor mechanisms are unknown. However, an increase in intra-alveolar pressure, by compressing the pulmonary capillaries, can increase the resistance to blood flow through them and have a decided effect on the pulmonary arterial pressure.

There is no simple linear relationship between the intra-alveolar pressure and the resistance to flow through the pulmonary vessels. Our studies on the effect of extravascular pressure on flow through vessels reveal a complex relationship which is discussed elsewhere.[43]

The pulmonary arterial pressure rises with the increase in intrathoracic pressure during expiration and falls during inspiration. (Fig. 2.) An increase in bronchomotor tone would augment this effect and provide an increased resistance to flow through the pulmonary capillaries. Pulmonary hypertension would ensue, being most marked during expiration.

When the left ventricle fails to pump away its venous return, pulmonary venous pressure rises and this in turn is transmitted to the pulmonary capillaries.[44] The structure of the pulmonary capillary is such that pulmonary edema is a natural consequence of a raised pulmonary venous pressure, unless an extravascular pressure is applied to these delicate

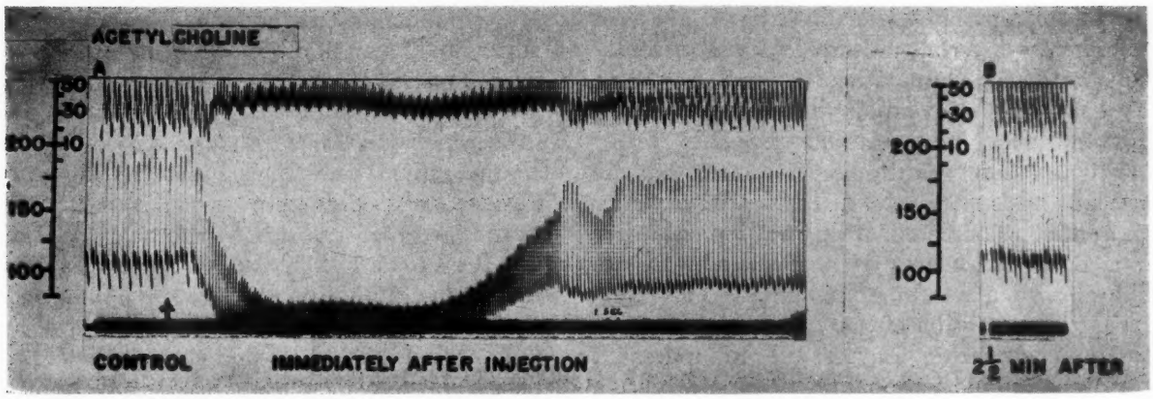

FIG. 3. Simultaneous recording of pulmonary arterial pressure (above) and systemic arterial pressure (below) in an unanesthetized dog receiving an intravenous injection of 0.25 mg. of acetylcholine. The characteristic systemic vasodilatation and fall in blood pressure is seen. The rise in pulmonary diastolic arterial pressure may be due to increased intra-alveolar pressure following the known bronchoconstrictor effects of this parasympathomimetic compound. Reproduced from Figure 4 of Friedberg, Katz and Steinitz.[45]

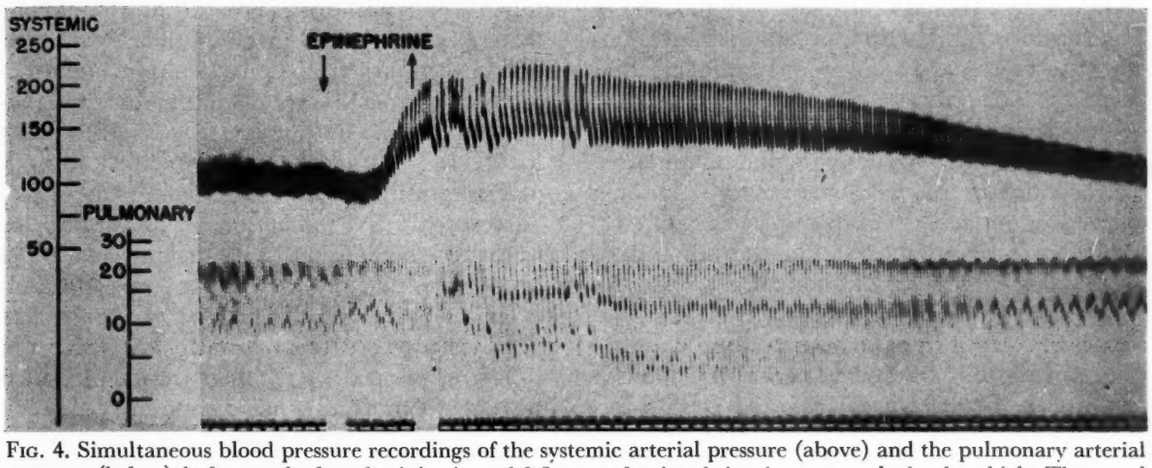

FIG. 4. Simultaneous blood pressure recordings of the systemic arterial pressure (above) and the pulmonary arterial pressure (below) before and after the injection of 0.5 mg. of epinephrine intravenously in the chick. The usual hypertensive effect of epinephrine is seen in the systemic blood pressure curve. Attention is called to the fall in the pulmonary diastolic arterial pressure during the period of action of the adrenalin. Reproduced from Figure 1 of Rodbard, Brown and Katz.[20]

vessels. This is apparently accomplished through the agency of a rise in intra-alveolar pressure. The raised pulmonary venous pressure is thus effectively transmitted to the pulmonary arteries. Supportive evidence for this view can be obtained from experiments with drugs which cause acute changes in pulmonary arterial pressures.

DRUGS AND THE PULMONARY CIRCULATION

The administration of drugs is known to produce effects on the pulmonary arterial pressure[45,46] which are difficult to explain on the basis of the older concepts. Thus acetylcholine[47] and histamine cause a transient rise in the pulmonary diastolic pressure. (Fig. 3.) It is suggested that elements of this rise in pressure are related to the increased bronchomuscular tone which these parasympathomimetic drugs excite,[48] rather than to a direct action on the pulmonary arterioles.[49,50]

In pulmonary hypertension, such as occurs in emphysema, the administration of bronchodilator drugs may result in a fall in pulmonary arterial pressure. Adrenalin, priscoline and tetraethylammonium chloride have been shown to lower the pulmonary vascular resistance.[4,5]

The normal pulmonary arterial pressure is so low that few agents cause it to fall. Under certain circumstances, however, the pulmonary arterial pressure may be lowered from normal values by adrenalin,[20] with dilatation of the pulmonary capillaries.[51] These results may depend in part on adrenalin-induced bronchodilatation with an associated fall in intra-alveolar pressure. (Fig. 4.)

More commonly adrenalin leads to a rise in pulmonary arterial pressure. It has recently been appreciated that the effects of adrenalin are often quite complex and under certain circumstances may lead to bronchospasm.[48] With large doses of this potent pressor agent the systemic resistance and arterial pressure may be markedly increased. If this is severe and prolonged, the left heart may be thrown into acute failure with a rise in pulmonary venous pressure.[52] Transmission of this heightened pressure to the capillaries may result in increased transudation and pulmonary edema may ensue.

EXPERIMENTAL PULMONARY EDEMA

A large variety of apparently unrelated experimental technics produce acute pulmonary edema. These include intravenous injections of large doses of adrenalin[52] or ammonium chloride,[53] intracranial compression[54] and injection of veratrine or fibrin.[55]

We suggest that these apparently diverse mechanisms may have a common denominator: the production of a relative sympathotonic state. All operate to increase sympathetic activity, and thus favor an increase in the amount of circulating adrenergic substances, or decrease parasympathetic tone. The effect is clear in the case of injected adrenalin. Ammonium chloride administration or the intracisternal injection of veratrine or fibrin causes profound central excitation and production of marked arterial hypertension, probably due to release of adrenalin congeners into the blood stream. Intracranial compression triggers the release of large amounts of nor-epinephrine into the blood stream.[56] The intracranial injection of veratrine, barium sulfate crystals or fibrin[55] also precipitates a marked epinephrine-like rise in arterial blood pressure.

Adrenalin in appropriate dosage produces an overloading of the left ventricle[52,54] and the simultaneous paralysis of bronchomotor tone. Acute pulmonary congestion ensues with accumulation of blood in the pulmonary veins and capillaries. Pulmonary edema follows from the simple mechanical rise in filtration pressure in the alveolar capillaries. If bronchomotor paralysis prevents a compensatory rise in the intra-alveolar pressure, transudation is unchecked and bubbling pulmonary edema can be expected to follow. Administration of adrenergic blocking agents such as benzodioxane or dibenamine inhibits the pressor effects as well as the pulmonary edema subsequent to injected adrenalin,[54] ammonium chloride[53] or intracranial fibrin injections or compression.[55]

Treatment of Pulmonary Edema. Positive pressure respiration has been shown to be useful in counteracting pulmonary edema. Here the mechanism is believed to be due to transmission of the increased pressure to the alveoli, forcing the transuded fluid back across the capillary membrane into the blood stream. In pulmonary congestion the widened vascular shadows and the opacities caused by pulmonary edema have been shown to decrease considerably immediately upon application of a heightened alveolar pressure.[57]

The classical emergency treatment of clinical pulmonary edema due to congestive heart failure utilizes the administration of morphine. The generally accepted mechanism of morphine action centers around its soothing effect in alleviating anxiety and dyspnea, thereby lowering the cardiac output and the left ventricular load.

The possibility that this opiate operates in part at least by its effect on bronchomotor tone must also be considered. Morphine is a potent bronchoconstrictor, acting to raise alveolar pressure and thereby producing an intrinsic positive pressure mechanism. This interpretation is supported by findings that the administration of a morphine-like compound (eukadol®) to patients in congestive failure resulted in clinical improvement with an *increase* in pulmonary arterial pressure.[58]

BRONCHIOLAR HYPERTONUS

The pathology of emphysema is commonly ascribed to a loss of *elasticity* of the lung[62,63] or to primary changes in the thoracic cage.[64] Microscopically, the destruction of alveolar septa and the paucity of capillaries are referred to as primary processes that decrease lung elasticity and increase resistance to blood flow through the lungs. The bronchiolar concept emphasizes that the increased expiratory resistance brought on by bronchomotor hypertonus may play a primary role in the pathogenesis of the disorder.

When bronchiolar tone increases, the expiratory rise of intra-alveolar pressure is enhanced because of air entrapment. This process may be cumulative with successive respiratory efforts until the lung is filled with air under tension. The alveolar capillaries are thereby compressed, some of them are obliterated and blood flows

through the lung with increased resistance. The alveolar entrapment of air reduces effective pulmonary surface area and gas exchange and thus explains cyanosis and hypoxia. Since acute hypoxia itself may cause a rise in intrapleural pressure[41,42] and pulmonary arterial pressure[2,6–8] a vicious cycle is established.* In severe hypoxia the effects of adrenalin are inhibited[59,60] and those of acetylcholine are enhanced,[61] thus furthering the bronchospastic tendency. The "rigidity" of the lung characteristic of this condition is therefore dependent on entrapped alveolar air. The elastic tissues of the lungs are therefore not the primary offenders but suffer from compression and tearing because of the primary bronchomotor disturbance. Right ventricular dilatation and hypertrophy will ensue in time if the increase in bronchiolar tone and pulmonary hypertension is marked and persistent.

Despite the prolonged high pulmonary arterial pressure the lungs at autopsy are seldom if ever the site of pulmonary edema; instead the lung is dry and tense, and usually does not collapse on opening of the chest. These facts serve to emphasize the important role of entrapment in the pathogenesis of emphysema and the eventual development of chronic cor pulmonale.

Therapeutic Considerations of Bronchomotor Tone. The bronchiolar tone concept helps to make rational certain therapeutic data on chronic cor pulmonale. If the airways could be opened and the entrapped air be permitted to escape, much of the disability of chronic cor pulmonale would be dissipated. Potent bronchodilators such as ephedrine, epinephrine and aminophylline have been used with success. The pulmonary arterial pressure falls despite an increase in cardiac output and a marked reduction in pulmonary vascular resistance is evident.[65] Unfortunately the bronchial and bronchiolar hypertonus is often marked and difficult to reverse, and anatomic consequences may have advanced to the point where limited pulmonary reserve remains. Changes in the bronchial mucosa and the accumulation of exudate may make even marked bronchodilation often of little value. By contrast, bronchoconstrictors such as morphine are strongly contraindicated in these chronic pulmonary and cardiopulmonary diseases.[66] The deleterious and sometime fatal action of morphine in these conditions has generally been attributed to its depressant effect on the respiratory center. The present thesis suggests that morphine produces some of these effects by increasing bronchomotor tone, causing alveolar air entrapment and paving the way to asphyxia.

TUSSIVE SYNCOPE

Tussive syncope often follows a paroxysm of coughing in older emphysematous patients.[67] The syndrome is associated with peripheral venous pooling, decreased cardiac output, falling systemic blood pressure and unconsciousness. Coughing has been shown to produce spasms of the bronchioles in man.[30,31] It is suggested that the reflex bronchiolar spasm and air entrapment induced in coughing results in a marked rise in intra-alveolar pressure and an increased intrapleural pressure. This interferes with the venous return to the left heart, as in the Valsalva maneuver. The limited blood volume returning to the right ventricle meets the enhanced resistance in the pulmonary capillaries and forward output diminishes sharply. Systemic venous pooling, hypotension and syncope result.

PULMONARY EMBOLISM

Experimental embolization with starch granules of the arterioles of a *single lobe* of the lung may result in a marked rise in pulmonary arterial pressure,[68] distention of the right heart and death in asphyxia in a few minutes.[69,70] Similar unexplained effects are sometimes seen clinically after repeated embolization. This effect can hardly be due to a loss of aerating surface of the lung since unilateral pneumonectomy does not significantly affect oxygenation of the blood.[23] The paradoxical effect of embolization of a small portion of the pulmonary bed resulting in tachypnea, pulmonary hypertension, cyanosis and death must therefore be explained on some other basis.

The pulmonary changes attendant upon minute embolism of a single lobe of the lung emphasize the important role of reflexes in the lung. It has been shown that embolic polypnea

* The direct central control of bronchomotor tone has now been clearly demonstrated. Perfusion of the dog brain with mixed venous blood caused bronchoconstriction. This was potentiated by eserine, and inhibited by atropine or cervical vagotomy. Hypercapnic blood caused bronchodilatation through a diminution of vagal tone. (DE BURGH DALY, M., LAMBERTSEN, C. J. and SCHWEITZER, A. The effects upon the bronchial musculature of altering the oxygen and carbon dioxide tensions of the blood perfusing the brain. *J. Physiol.*, 119: 292–341, 1953.)

is not related to circulatory conditions of the lung, heart or general vasculature since it can be evoked by embolizing a bloodless lung.[69] By contrast, occlusion of the main stem of one pulmonary artery has no effect on respiratory rate or systemic blood pressure. After embolization of an innervated lung, polypnea ensues and occlusion of its pulmonary artery does not reduce the rate of breathing. Section of the pulmonary branches of the vagus abolishes the polypnea. It is more difficult to inflate the embolized lung than the normal lung.[71] The intrapleural pressure is increased markedly after embolism.[72] It would appear from these data that an important feature of the disturbance is the production of a reflex bronchiolar spasm in the embolized lung segment, with radiation of this effect to the remainder of the pulmonary parenchyma. Evidence is available which suggests that stretching of the precapillary arteriolar receptors by the fine emboli sets off generalized reflexes which may be normally adapted to prevent pulmonary engorgement.[69] Increased bronchiolar tone results. If this tone is excessive, alveolar gas exchange will be impeded with the development of cyanosis, and acute right heart failure may finally ensue from the suddenly elevated load on the right ventricle.

KYPHOSCOLIOSIS

The idiopathic emphysema and chronic cor pulmonale seen in patients with kyphoscoliosis and other conditions with a markedly reduced pulmonary parenchyma may also have their pathogenesis, at least in part, in increased bronchomotor tone. The cardiac output is normal or even elevated in these patients, even though the pulmonary vascular bed is markedly restricted. It is suggested that a normal or hypernormal stroke output pumped into a markedly reduced lung field may produce *relative* pulmonary engorgement and excite a reflex increase in bronchomotor tone. Long persistence of such increased bronchomotor tone will lead to emphysema, chronic cor pulmonale and finally to right ventricular failure. The fact that kyphoscoliotics and other patients with a reduced pulmonary bed cannot tolerate bronchoconstrictors such as morphine supports this concept.

PAROXYSMAL NOCTURNAL DYSPNEA VERSUS CARDIAC ASTHMA

Clinical experiences with the management of patients during acute attacks of congestive heart failure have posed a number of unsolved problems in cardiopulmonary interrelationships. Left ventricular failure due to valvular disease or systemic hypertension can operate to raise the pulmonary venous pressure to levels adequate to produce pulmonary edema. Yet frank pulmonary edema does not necessarily ensue at once. Instead, the congestion is transmitted to the right heart, giving rise to the dictum: "The most common cause of right heart failure is left heart failure." The failure of pulmonary edema to occur prior to overloading of the right heart has not been satisfactorily explained. Yet the structure of the lung is such that unless some mechanism is available to protect it from transudation, right heart failure could not develop later. It is suggested that this mechanism resides in a heightened intra-alveolar pressure.

When the pulmonary capillary pressure is raised excessively, fluid will escape into the alveoli and bubbling rales may be heard. At other times, or even during the same attack, the patient is in severe dyspnea but asthmatic pipings, rather than bubbling rales, are heard. These two clinical pictures have often been lumped together under the name of "paroxysmal nocturnal dyspnea," often with the qualifying parenthetical expression, "cardiac asthma."

The bronchomotor concept suggests that in these clinical conditions two markedly opposed but closely related situations are operating. Inability of the left ventricle to pump away the pulmonary venous return leads to progressive pulmonary congestion, transudation and edema. A reflex bronchoconstriction may be initiated, producing a protective intrinsic positive pressure effect.* The increased pulmonary resistance thus created operates to transfer the burden to the right heart.

Disturbances in respiration (dyspnea, tachypnea and active expiratory effort) may be outward manifestations of these compensatory mechanisms. In support of this interpretation

* Analysis of pulmonary arterial and wedge pressure curves supports the concept of the important role of bronchomotor activity in the prevention of pulmonary edema. In normal man the inspiratory and expiratory fluctuations in pulmonary arterial pressure are symmetrical and minimal. In congestive failure or pulmonary congestion due to other causes the expiratory rise in pulmonary arterial pressure may be marked (10–20 mm. Hg). Further, the expiratory effect is prolonged while inspiration is of short duration, with a consequent limited period during which the pulmonary capillaries are deprived of their positive pressure support.

are the findings that in congestive failure the intrapleural pressure is elevated,[63] as is the pulmonary arterial pressure. With the transuded fluid forced back out of the alveoli the lungs become dry, and piping expiratory rales will be heard. If bronchiolar tone becomes excessive, as may occur especially in hypersensitive individuals or in those with chronic bronchitis, an asthmatic tendency may supervene. The striking effects of such therapeutic regimens as venesection and mercurial diuretics may operate by reducing pulmonary congestion and thus lessening the need for the elevated bronchomotor tone. Viewed physiologically, paroxysmal nocturnal dyspnea (pulmonary edema) may therefore be considered as the antipode of cardiac asthma rather than its synonym, even though both may appear during the same attack.

The structural changes in the lungs in mitral stenosis[73] give evidence that the markedly congested pulmonary capillaries bulge into the alveolar spaces. No definite changes are found in the elastic tissue but the alveolar diameters are increased from the normal of 12–20 μ to 20 to 50 μ in this condition. Despite the almost generalized congestion some areas of emphysema without congestion may be present. The possible relation to bronchomotor mechanisms is suggested by the marked hypertrophy of the bronchiolar musculature in chronic cardiac disease and in emphysema.[74] The highest degree of hypertrophy is reported to occur in pure mitral stenosis and this is especially striking in the musculature of the alveolar passages in which the muscles are two and one-half times their normal size.[74]

The adequate adjustment of bronchomotor tone to the demands placed by the danger of edema must be balanced against the cost of the increased load on the right ventricle. This precarious balance may be the basis for some of the difficulties in the management of congestive heart failure. Thus left ventricular failure must be ransomed by overloading of the right heart and raising the specter of failure of the lesser chamber. Treatment must obviously be carefully regulated. In bubbling pulmonary edema the treatment of choice is aimed at an increase in bronchomotor tone: morphine, with digitalis as a cardiotonic drug. Where pulmonary edema precipitates excessive bronchospasm (cardiac asthma), bronchoconstrictors may not prove of value and, instead, bronchodilators such as aminophylline and others *may* be indicated.

SUMMARY

A consideration of the structure and function of the lungs has led to a re-analysis of the factors regulating blood flow. The present study reviews the physiology of respiration and calls attention to extravascular mechanisms in the approach to the general physiology of the pulmonary circulation. In particular, the hydrodynamic balance in the alveolar capillaries in pulmonary edema, chronic cor pulmonale and congestive heart failure is analyzed. Special stress is laid on the role of the bronchomotor apparatus as an important factor in the regulation of pulmonary hemodynamics in health and disease.

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Seminars on Neuromuscular Physiology

Clinical Problems in Neuromuscular Physiology*

D. DENNY-BROWN, M.D.

Boston, Massachusetts

THE florid forms of the classical types of neuromuscular disease can be readily distinguished by inspection, with the addition of simple tests of sensation, motor performance and reflexes. Yet the clinician frequently encounters atypical and minor disorders which present problems insoluble without further exact knowledge of the conducting mechanism of nerve and the contractile mechanism of muscle. The development of electrical stimulation by Duchenne and Erb was a notable advance in their time. The introduction of muscle biopsy by Duchenne was premature, and only after staining methods were greatly improved, and considerably more knowledge had been acquired by routine pathologic methods, has muscle biopsy become a standard procedure. The electromyogram has now become generally available, providing direct registration of the arrival of nerve impulses in the muscle fibers. Even with these additional facilities, however, disorders of muscular contraction in man present many difficulties which stem either from inadequate methods of defining the problem or from insufficient knowledge of the fundamental physiology of nerve and muscle.

In outlining the physiologic problems seen in the clinic we might begin with the relatively simple situation presented by the events following the traumatic section of a muscular nerve.

DEGENERATION AND REGENERATION OF A MUSCULAR NERVE

The flaccid paralysis and progressive atrophy of a muscle deprived of its motor nerve supply is common knowledge. The paralysis naturally results from the absence of nerve impulses, but the atrophy has many debatable aspects. The rate of atrophy is very variable. Some muscles (e.g., laryngeal muscles) virtually disappear in a few weeks, others (e.g., vastus medialis) lose bulk only very slowly, still being fleshy many months, even two or more years, after denervation. Atrophy is defined as a loss of size without actual change in structure. In a muscle fiber this necessarily means a loss of some of the hundreds of striated myofibrils which normally distend each muscle fiber. The fiber then lessens in diameter but presents no other change except that the muscle nuclei are more plump, no longer are flattened against the sarcolemma and are slightly increased in number. Since physiologic hypertrophy resulting from repeated training or use of a muscle is an increase in diameter of each muscle fiber due to increased number of myofibrils within it, it has been natural to attempt to prevent muscular atrophy by regular electrical stimulation of denervated muscles. The effects of such stimulation are disappointing, even in experimental studies, in which it seems that only the initial loss of weight may be retarded by electrical treatment.[1–3] The muscle in neural atrophy presents a continued but variable spontaneous activity of the individual fibers in the form of irregular, very small contractions called fibrillation, visible only when the surface of the muscle is laid bare, or is very superficial as in the tongue. Prevention of such fibrillation by administering quinidine experimentally does not either prevent or enhance atrophy.[4] On the other hand, types of nerve block which do not interrupt the axis cylinders

* From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School Boston, Mass.

of the nerve, as in ischemic (tourniquet) nerve paralysis,[5] are not associated with atrophy beyond that which occurs with disuse.

In normal muscle any form of trauma which damages only part of the muscle fiber and its sarcolemmal membrane is followed by regeneration from the intact remainder of these structures; so that, unless the fibrous framework of the muscle is destroyed, new sarcolemmal tubes are formed and filled with myofibrils.[6,7] In comparing the histology of this process when the tendon was sectioned at the same time as the damage was inflicted with the response to the same damage in muscle with intact tendon, we[8] found the speed of regeneration in the latter circumstances greatly increased. Tension is therefore considered to be an important factor in stimulating the production of myofibrils and particularly in their maturation.

Besides natural tension an intact nerve supply is also essential for the production and maturation of myofibrils. In denervated muscle passive tension appears to initiate degeneration of the muscle fibers rather than stimulating the production of myofibrils. Any form of physical trauma to denervated muscle after the first month results only in the formation of sarcolemmal bands without any myofibrils, and these then rapidly fragment and degenerate.[7,8] The process of degeneration and disappearance of the fibers of some muscles which becomes added to the process of atrophy in some denervated muscles is probably due to overstretching.

The initial atrophy and loss of myofibrils following nerve section is part of a general process which is associated with increase in excitability and increased sensitivity to substances which excite muscle. Spontaneous fibrillation is related to this process and free acetylcholine is its probable cause. The mechanism of this change is not understood. The region of the motor end plate retains its cholinesterase activity for a very long period. The change is associated with a loss of potassium content, but this is thought to be part of the change rather than the cause of it. There is no immediate reaction in the interstitial tissue except that after some months, when degeneration of some fibers is beginning, abnormal numbers of fat cells begin to appear among the muscle fibers, eventually replacing them.

In the clinic the presence of neural atrophy can be confirmed by the electrical reactions, as originally defined by Erb. Within ten to fourteen days after nerve section, when the nerve endings have finally disintegrated, the ability to excite the muscle by a faradic electrode over the motor point is lost, and a galvanic current now excites the muscles at lower amperage. This difference, called the "reaction of degeneration" is much easier to determine and much more reliable than attempts to measure the "chronaxie," the time factor in the critical voltage strength-duration formula of electrical stimulation. Chronaxie is greatly influenced by skin resistance, and in addition is more suited for very excitable tissue such as nerve. When regenerating nerve fibers reach the atrophic muscle, the sensitivity to galvanic current suddenly lessens, fibrillation ceases, and sensitivity to acetylcholine decreases, many days before ability to contract the muscle by willed effort returns. Only at a later date does measured chronaxie lessen and the ability to excite the muscle by faradic current return.[9] This is because the newly regenerated nerve fibers are at first very small and difficult to excite, even after they have commenced carrying impulses which can result in contraction of muscle fibers. Chronaxie and the faradic current used in this way measure the excitability of the terminal nerve filaments, whereas the earlier changes in the muscle fiber reflect something which it derives from anatomic continuity with the nervous system, even before nerve impulses can cause contraction.

The electromyogram of a muscle paralyzed by nerve section reveals only the very small irregularly repeated series of very fast spike potentials which accompany fibrillation. (Fig. 1B.) The rhythmical series of larger regularly repeated potentials, which show natural activity of the motor nerve cell and its group of muscle fibers ("motor unit") (Fig. 1A) are lacking. Fibrillation activity is readily provoked by trauma such as moving an electrode. If the patient is completely relaxed, it may be difficult to demonstrate but it is always present in some degree. In nervous, tense patients it may be very prominent owing to the presence of acetylcholine in the circulation. When regeneration occurs the first motor unit potentials to appear are very complex, being multiphasic,[10] probably owing to the slow conduction of the thin newly regenerated branches of the parent nerve fiber, so that the same nerve impulse reaches some muscle fibers later than others. The duration of single action potentials may therefore have significance in distinguishing neural atrophy

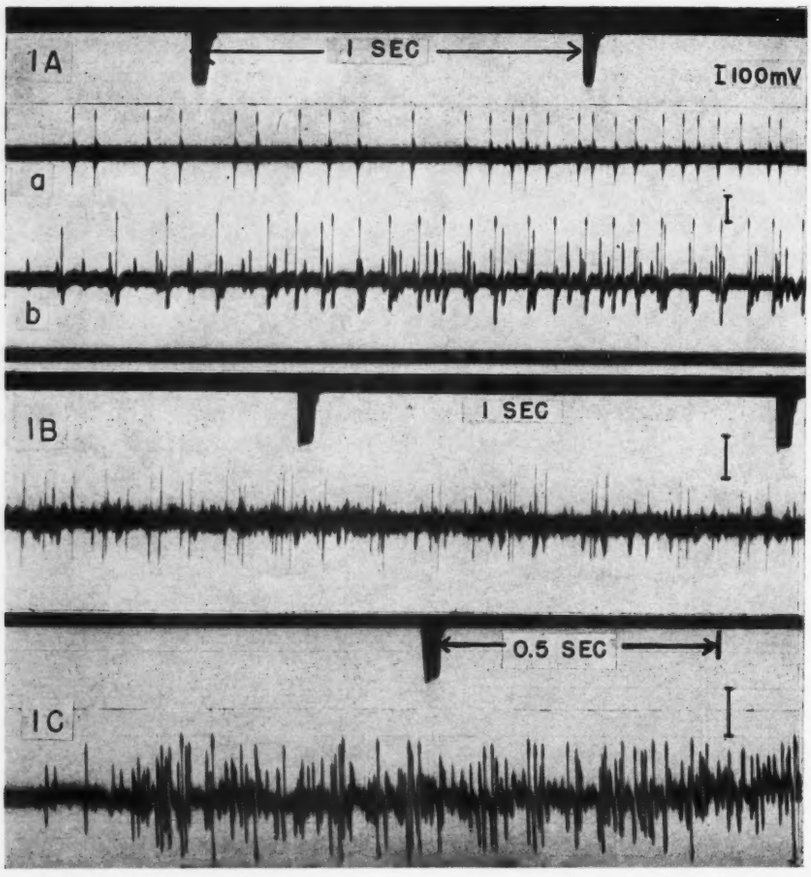

FIG. 1. Electromyographic records made with concentric needle electrode, Grass amplifying system, and Westinghouse oscillograph, recording on bromide paper. All records read from left to right. The speed of recording is indicated by the time interval marked at the top of each record, or the first of a set of records at the same speed. The amplification is indicated by a vertical line showing 100 microvolts. A, the action potentials in the thenar eminence of a normal subject recorded by two electrodes (traces *a* and *b*) in the same muscle during a gradual willed movement. Seven motor units begin discharging rhythmically, one in lead *a* and six in lead *b*. B, fibrillation potentials in a paralyzed muscle (polyneuritis). C, onset of voluntary contraction in the very atrophic trapezius muscle in muscular dystrophy.

from other types of muscular disorder, but to measure this change extremely accurate and rapid recording is necessary.

MUSCULAR DYSTROPHY

The essential feature of muscular dystrophy is that a slow degeneration of muscle fibers occurs, fiber by fiber, throughout an affected muscle in spite of intact anatomic connection with nerve. Whereas in denervation atrophy all the muscle fibers supplied by any severed nerve fiber (motor unit) are in the same stage of atrophy, one motor nerve fiber in muscular dystrophy supplies muscle fibers some of which are affected, some not. Those which are affected present disintegration of myofibrils and eventually break up into tubes which contain no myofibrils, in the same manner that ultimately occurs in denervation atrophy. In dystrophy this liability to degeneration is much greater in some muscles than others, and in general is greatest in those which are the slowest to exhibit denervation atrophy. A histologic feature called fiber-splitting (a normal fiber splitting into two normal daughter fibers within the same sarcolemma) in dystrophic muscles indicates that some abnormality has been present since fetal life. In dystrophy trauma is not followed by regeneration as in normal muscle[7,11] indicating that the process of forming new myofibrils is defective in the same sense that occurs late in denervation atrophy. Such myofibrils as are formed contract normally, both in the physical and biochemical aspects of the contraction process. The unknown substance which an intact nerve gives to muscle and which enables regeneration of myofibrils is ultimately ineffective in some fibers in muscular dystrophy in spite

of intact nerve endings. The power of regeneration of muscle is also lost in a form of chronic polymyositis[11] which has a certain similarity to dystrophy. In all other forms of polymyositis regenerative activity is very active,[7] particularly in dermatomyositis, and experimental myositis due to vitamin E deficiency and Coxsackie virus infection. These disorders should not be confused with dystrophy.

Since the residual muscle fibers of dystrophic muscle contract normally on stimulation of the motor nerve, a response to faradic stimulation is retained as long as muscle fibers remain, and its strength is proportional to the remaining bulk of the muscle. The chronaxie is unchanged. It is not known if partially affected muscle fibers respond abnormally to galvanic current, for there are very few in this stage at any one time, but fibrillation is not present in the electromyogram. The motor unit potentials in the EMG are all small in severely affected muscle, for the number of muscle fibers per unit is reduced. (Fig. 1C.) In addition they are somewhat more brief if the duration of each potential is accurately measured.[12] No other change has been demonstrable. The characteristic biopsy finding is fibers in all stages of chronic degeneration scattered through the muscle.

If the only altered physiology in the muscular dystrophy is in the slow process of repair of myofibrils the only way of sampling this is that of double biopsy—a local injury to muscle fiber at biopsy, followed by a second biopsy ten to sixteen days later to sample the repair process.[7] This is a somewhat clumsy method for routine use and we hope to improve it.

PHYSIOLOGIC HYPERTROPHY

The process of athletic training clearly demonstrates that repeated use of muscles can increase their size. Such physiologic hypertrophy is an increase of myofibrils in each muscle fiber. The supporting tissue, in the form of endomysial tubes of reticulin, are distended by the larger fibers, giving the muscle a tight rubbery elastic feeling even in complete relaxation. This change in consistency is the opposite to the flaccidity of an atrophic muscle, but it is in no way related to spasticity which is a quality appreciated by passive stretch. Hypertrophied muscle offers no resistance to passive stretch appreciable to the examiner. A factor appreciable only in rapidly alternating powerful movement is slowness in relaxation, the "muscle bound" state of the athlete early in training, but this is also an independent quality related to factors such as speed of activation of antagonists and possibly vascular supply. Physiologic hypertrophy is not associated with any known change in excitability or EMG pattern, except a liability to muscle cramps which will be discussed later.

As a result of paralysis of some movements compensatory muscles show physiologic hypertrophy. In benign forms of muscular dystrophy, for example, the deltoids may hypertrophy to compensate for weak trapezius muscles. Such a change does not have the same prognostic significance as the "pseudohypertrophy" of the calf muscles of severe forms of dystrophy, which is due to an accumulation of fat in the connective tissues of the muscles. In poliomyelitis and in chronic polyneuritis such as Charcot-Marie-Tooth's disease the unaffected muscle fibers is an affected muscle will exhibit enormous physiologic hypertrophy, presenting a biopsy picture that has been confused with dystrophy. Such muscles show no change in excitability traceable to the hypertrophy.

THE NEUROMUSCULAR JUNCTION

Although much has been written concerning the special susceptibilities of the junction between nerve and muscle, the application of current hypotheses of physiology to the disorders of neuromuscular transmission seen in the clinic fails to explain many common features of these disorders. Since the demonstration of humoral transmission by acetylcholine at the neuromuscular junction by Dale, Feldberg and Vogt,[13] it has commonly been assumed that its disorders could be fully understood in terms of inadequacy of acetylcholine or overaction of cholinesterase. To examine the difficulties that occur we must first state a general conception of the neuromuscular junction. It is seen under the microscope as the motor nerve ending. The terminal arborization (telodendria) of the axis cylinder is embedded in sarcoplasm of the terminal Schwann cell (teloglia), which in turn lies in grooves in a complex layer or mat (the subneural apparatus of Couteaux).[14] This last layer appears to be continuous with the limiting membrane of the muscle cell (sarcolemma) and separates the neural part of the end-plate (telodendria and teloglia) from the muscle sarcoplasm and muscle nuclei which bulge under it. The contractile elements or myofibrils lie closely packed in the muscle fiber,

surrounded by scant sarcoplasm which is continuous with that of the end-plate.

A nerve impulse arriving at the terminal arborization sets up there an electric potential known as the end-plate potential. As the end-plate potential rises it sets off a muscle action potential which is then rapidly transmitted along the muscle fiber, and in doing so initiates a contraction in the whole length of all the myofibrils.[15] There is then a very brief interval of time, the refractory phase, when a second nerve impulse or end-plate potential may fail to fire a second muscle fiber potential. The refractory phase evidently represents a process of restitution of ionic balance, and is more brief in nerve than in muscle.

Muscle and nerve both possess an internal medium rich in potassium separated from the sodium-rich environment by the cell membrane. In recent years very considerable advances have been made in the understanding of the mechanism of excitation of muscle and nerve, particularly in the genesis of the action potential and end-plate potential.[15–18] There has resulted a fairly complete accounting of the cycle of permeability changes in the various membranes of muscle and nerve, incorporated in what is called the "ionic hypothesis." The interior of the nerve or muscle is maintained in a state of electrical negativity, partly by an excess of potassium ions within the cell, but in greater degree by the transport of sodium ions out of the fiber. There is a constant tendency of sodium ions to enter the fiber and a continuously active process which transports them outward across the cell membrane (the "sodium pump"). The action potential which accompanies activity has been quantitatively related to an inward shift of sodium, which contributes the negative spike of the potential, and a slower smaller outward shift of potassium, which results in the small positive after-potential. Each nerve impulse releases a very small quantity of acetylcholine which, by producing a momentary increased permeability of the muscle membrane at the end-plate, generates the end-plate-potential.[19] This in effect short circuits the surrounding muscle membrane and thus generates a wave of excitation, with its own action potential, on the surface of the muscle fiber. Ionized magnesium and calcium are necessary for the contractile features of actomyosin, which is assumed to underlie the contraction of myofibrils, and in addition are essential for the proper stabilization of the potassium-sodium balance of ionized excitable membranes. The part they play is undetermined. It is clear, however, that the sodium pump requires an active metabolic process, not only for the maintenance of the resting negative potential of the inactive muscle or nerve contents, but for its restitution following each wave of excitation.

The myofibrils can be caused to contract by a fine needle electrode, or by a mechanical stimulus, without setting up a propagated potential wave in the sarcolemma.[20,21] The contraction then either remains localized or is propagated slowly along the contents of the muscle fiber without action potential. This phenomenon can often be seen when a fasciculus of muscle is pinched momentarily (Schiff's phenomenon) and is prominent as a localized swelling in cachectic persons when a muscle is pinched or percussed ("myoedema").[27] For practical purposes we can therefore regard the sarcolemma as the normal transmitter of the nerve impulse, or end-plate potential, to the whole muscle fiber so that it contracts efficiently.

The pharmacology of the end-plate is complex, but for the present purpose we may take as a starting point the findings of Burns and Paton[23] which indicate that the portion of the muscle membrane at the end-plate maintains an independent polarization. The means by which this is maintained is unknown, but there is evidently an equilibrium which can be broken down in either of two directions. The process of breakdown is associated with the initiation of impulses in the muscle membrane, and normally is the result of the end-plate potential. A small amount of acetylcholine, such as might normally be produced in the teloglia by one nerve impulse, depolarizes the end-plate muscle membrane sufficiently to set up one muscle potential and so cause one twitch of the fiber. An excess of acetylcholine causes rhythmical twitching. A large amount of acetylcholine completely depolarizes the muscle membrane near the end-plate so that it no longer transmits nerve impulses. The same type of depolarization is, however, produced by decamethonium, which also produces fascicular twitching rapidly followed by a nerve block, and can also be set up by passing a current through the muscle fiber, with the cathode at the end-plate region. Such depolarization is antagonized by curare, pentamethonium or a current with anode at the end-plate region. All these alone can

depolarize the end-plate region in the reverse direction, also producing a neuromuscular block, which can be antagonized by acetylcholine or decamethonium. With either type of block the muscle fiber may be excited directly by stimulating the independently polarized muscle membrane.

Cholinesterase was found to be present in the subneural apparatus, in which Couteaux showed its presence by the Janus green method[14] which also stains some of the sarcolemma on either side of the end-plate. The apparatus and its vital staining persist for a long period after denervation of the end-plate. Koelle and Friedenwald[24] have now shown this location of cholinesterase by a more specific staining method. The presence of cholinesterase appears to be necessary to ensure rapid destruction of excess acetylcholine so that the muscle may respond only once to one nerve impulse.

Ionized potassium must play a large part in the polarization of the various membranes of nerve, subneural apparatus and muscle, but the relative importance and site of action of ionized calcium, magnesium and sodium in these different membranes is at present unsettled. Nor is it possible at present to offer any satisfactory view of the action of quinine, quinidine, 2-4-D, and other substances which disturb the mechanism of depolarization. Quinine for example depresses conductivity yet has an anti-cholinesterase effect. Its chief clinical usefulness is derived from its property in lengthening refractory phase, presumably by slowing the recovery process after breakdown of polarization in muscles or nerve. In this way it is useful in lessening the repeated discharges of myotonia and muscle cramps. In terms of what is known of the end-plate mechanism it might be expected that acetylcholine, or anti-cholinesterases, will combat mild degrees of the block caused by curare and this in fact happens.

The electromyogram in *myasthenia gravis* shows two abnormal features. At the beginning of a contraction there is the usual asynchronous burst of the potentials of many motor units, but the numbers of units, and the corresponding intensity of accompanying muscular contraction, rapidly decline to reach a relatively steady level of discharge, beyond which decline is slower. In this latter period the motor units drop out of contraction one by one, and critical recording may reveal that before a unit finally fails the height of the spike fluctuates a great deal, indicating that the number of muscle fibers responding to each nerve impulse in the corresponding nerve fiber is varying.[25,26] This would indicate that the failure developed independently in each of the nerve endings supplied by the nerve fiber. As the effort to contract the muscle continue, some muscle fibers continue to respond normally to the nervous discharge rhythms, and these fibers are presumably unaffected. If a special effort is requested, a new and poorly sustained burst of discharge occurs. Close inspection of the action potentials shows that these are not units paralyzed by the early part of the effort, but are new motor units that respond only when a special effort to contract a muscle is made. Even in the normal person there are motor units that respond only with intense effort, and these may be seen after the partial motor neurone or nerve paralysis produced by poliomyelitis or trauma. This phenomenon and the restriction of the typical muscular weakness to the bulbar or extraocular musculature in many cases make it difficult to get accurate information as to what happens to any particular motor unit.

Much has been made by some of the Wedensky phenomenon in myasthenia gravis. When nerve is experimentally partially blocked, so that the recovery phase (refractory period) is prolonged but still present, the first of a series of rapidly repeated impulses will get through, but the second falls into the relative refractory phase of the first, and becomes a subnormal impulse which fails to excite the muscle with its still longer refractory period. The result of a series of impulses at critical frequency of stimulation will then be a single twitch of the muscle. Pritchard[27,28] identifies the first large twitch of contraction of myasthenic contraction with the Wedensky phenomenon, and notes that it may occur with rates of stimulation of 80 a second, whereas it should not normally be evident with rates below 800 a second. The rate of neuronal discharge with willed movement is however seldom more than 50 impulses a second. In our own investigations of myasthenic muscle we have found that the initial failure is the result not of one excitatory impulse reaching the muscle but of several in each unit concerned. This is no longer explicable in terms of the Wedensky phenomenon, which allows only the first impulse through the blocked region.

In severely affected muscles this type of early failure with continued effort is very striking. (Fig. 2.) In addition, a region of muscle where

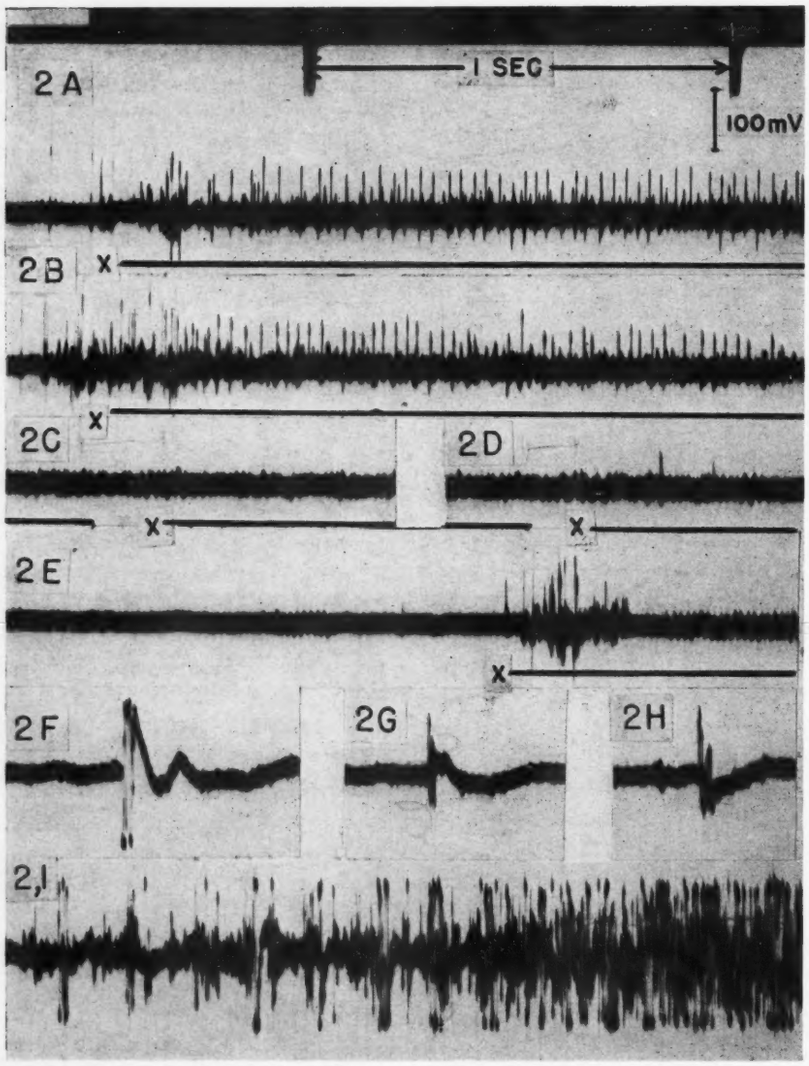

FIG. 2. Myasthenia gravis. Selected pieces of record from the brachialis anticus muscle in a very severely affected patient. A, result of an effort to flex the elbow steadily, beginning at *x*. After maintaining the effort for two seconds and relaxing for two seconds the effort is renewed in (B) at *x* and this time is continued for nine seconds. C, begins four seconds after (B) and shows failure of all units near the electrode. At *x* in (C) an additional effort is requested, without effect. At *x* in (D), two seconds after (C), an additional effort is again requested, with resultant one beat in one unit. E, the tracing just as the effort was relaxed. At *x* in (E) the effort is again made after 1.2 second of relaxation. A renewed burst of discharge is seen. F, G and H, fasciculation following 3 mg. prostigmine subcutaneously. I, shows attempted voluntary contraction which was still very weak.

all the units have failed shows no recovery of discharge as long as the effort is continued in spite of attempt of the patient to make an extra effort. Yet relaxation of the effort, and its renewal after as short an interval as one second (Fig. 2E) results in a renewal of discharge and renewed failure. As long as the patient continues the effort the units that have failed do not begin to discharge again. The failure is usually sudden, and it is only units that fail after more prolonged effort that show variation in height of action potential (as in Figure 2B). The situation in myasthenia gravis demands a *progressive* type of conduction block which requires a certain number of impulses to produce it, and which is *maintained* by nerve impulses. The whole clinical aspect of the paralysis in this disease points to the presence of a cumulative process depending on the arrival of nerve impulses, presumably an abnormal metabolite. This cannot be a muscle metabolite because it can be present in muscles that do not contract, and because the progressive failure of muscles is different from the painful process of fatigue even when the circulation is

occluded. We therefore postulate an abnormal neural metabolite, likely to be produced locally only in affected muscles, for we have not been convinced of a general effect from attempted use of one muscle group unless the myasthenic affection is generalized and severe. Only then have we seen exercise of one arm affect the ability to contract the other.

The absence of effect of attempted innervation of one muscle group in weakening other muscle groups in mild myasthenia gravis is in our opinion probably quantitative. Evidently active innervation of a large bulk of affected muscle and the availability of a susceptible test muscle are required. The response can be demonstrated in the absence of the thymus gland. The phenomenon is of special importance when the respiratory musculature is critically affected, for we have then seen attempted exercise of a limb muscle precipitate respiratory failure in two patients. We suspect that this is the mechanism of sudden death in myasthenia, for often the critical state of respiration can only be appreciated by recording the tidal air on a spirometer and showing its approximation to maximal inspiration.

In all myasthenics it is soon apparent that some of the paralysis does not recover with rest, and some of this paralysis is not reversed by prostigmin. Yet there is no degenerative change in the muscle or nerve endings, and such muscles may recover completely in a natural remission of the disease after weeks or months of paralysis. Prostigmin is an efficient anti-cholinesterase. The presence of fasciculation in such a muscle, and of multiple reduplication of action potentials in motor units which have recommended discharge under the influence of prostigmin (Fig. 2D) shows that acetylcholine is then being released in excess amount at the nerve endings. This must mean that defect in production or utilization of acetylcholine is not the cause of myasthenia.

The effect of anticholinesterases in neutralizing the milder degrees of myasthenic weakness shows that the defect is in the end-plate mechanism, and we must continue to search for a "curare-like" substance, probably produced by nerve impulses. Its existence is strongly supported by the transitory severe myasthenia in the newborn child of a myasthenic mother reported by Geddes and Kidd.[29] Another instance has been recorded by McKeever.[30]

Periodic paralysis also presents a problem in neuromuscular transmission. In this disease there is a liability, commonly familial, to attacks of paralysis of the limb and trunk muscles, rarely affecting the muscles of respiration and those of the cranial nerves. Aitken et al.[31] and Gammon and his associates[32,33] independently found that in their cases an attack of paralysis was associated with a fall in the level of serum potassium and could be relieved by administering potassium salts. The paralysis is frequently present on awakening from sleep, and may be provoked by inducing water diuresis, or by the administration of glucose or epinephrine, all of which circumstances may be associated with lowering of serum potassium.[33] During such attacks the excretion of potassium also fell, without change in serum level or excretion of sodium. These changes reviewed by Talbott,[34] have been confirmed by others. Although these studies pointed to some periodic disorder involving the withdrawal of large quantities of potassium from circulation, it was apparent from the first that the absolute level of serum potassium did not measure the liability to paralysis. Procedures which lower the serum level of potassium do not produce attacks in some families,[35,36] and the most complete investigation of one large family by Tyler et al.[37] has shown no change in serum potassium level in the attacks in this family. Types of attack have long been known when the failure involves only small asymmetric groups of muscles.[35,38] In the case of Pudenz et al.[39] occlusion of the vessels to one limb did not prevent that limb from sharing the recovery induced by giving potassium intravenously into the other arm, but this experiment is complicated by the effect of anoxia in causing movement of potassium. Heart muscle is much more sensitive than skeletal muscle to hypo- or hyperkalemia; and although some sufferers from family periodic paralysis show signs of cardiac disorder during an attack, many do not.

In the cases of family periodic paralysis we have seen the affected muscles are completely inexcitable by electrical or mechanical means during an attack of the disorder. Electromyographic and excitability studies during the onset and recovery of paralysis have not been made, but the loss of excitability points unmistakably to depolarization of the muscle membrane. Whether the myofibrils still show localized excitability is not known, but certainly a propogated twitch of an affected muscle cannot be elicited, and contractility is probably lost as

well as excitability. On the other hand hypopotassemia of the kind observed to result from chronic nephritis, in the course of treatment of diabetic coma, in overtreatment with desoxycorticosterone and from the loss of large quantities of gastrointestinal fluids leads only to muscle weakness. Coarse fascicular twitching and tetany are more prominent than the associated muscular weakness. These latter symptoms point to interference with neural excitability and will be discussed separately. Severe experimental potassium depletion in man is not associated with symptoms.[40]

The paralysis of periodic paralysis is more completely imitated by hyperpotassemia (hyperkalemia), although then cardiac changes dominate the picture. In cases such as those described by Finch, Sawyer and Flynn[41] the distribution and course of paralysis is precisely that of periodic paralysis. The only difference is that the muscles have been reported in one case to respond by a twitch to percussion at the height of the paralysis. An obvious possibility that is difficult to test is that the primary factor in an attack of the disease is an alteration of the muscle proteins such as to bind potassium in the muscles, and thus drain ionized potassium from the tissue fluids and the liver during an attack. This appears to be the only hypothesis which can offer a plausible explanation for the complete depolarization of the membrane of skeletal muscles and at the same time account for the variable changes in serum potassium level, and ability to affect muscles asymmetrically. The vacuoles which have been observed in biopsy sections of the muscle fibers by several investigators presumably reflect the severe osmotic change which would be associated with an episode of severe ionic displacement.[7] After some years the muscles most affected may show some atrophy, and this may be taken to reflect only the end result of repeated minor damage in some of the muscle fibers.

Several toxins may affect neuromuscular conduction. The best known are botulinus toxin, and that produced by the bites of certain ticks and snakes. The only one of these that has been closely investigated is *botulinus toxin*, of which the action differs from that of curare in leaving the muscle excitable by acetylcholine[42,43] although prostigmin is ineffective. The nerve conducts normally. This indicates an action on the mechanism of release of Ach by the nerve terminal. The extraocular and cranial muscles are more sensitive than those of the limbs and the paralysis may closely resemble myasthenia gravis. Acute thyrotoxicosis may also be associated with a similar syndrome, some cases being relieved by prostigmin[44] and some not.[45] In the absence of more certain knowledge of the factors involved the presence or absence of reaction to prostigmin does not enable us to reach any firm conclusions as to pathogenesis, except that there are several distinct kinds of neuromuscular block.

MYOTONIA

The phenomenon of myotonia is a lasting painless residual contraction in some of any group of muscle fibers which have been thrown into contraction. Myotonic contraction is associated with fine action potentials of the type seen in the fibrillation of denervation atrophy, in fast rhythms of 25 to 100 a second, each indicating independent activity of a single muscle fiber.[7] The resulting confusion of fibrillary rhythms can be seen to begin 0.1 to 1.5 seconds after the onset of the usual innervation potentials, or of direct stimulation of the nerve,[7,46,47] or muscle. The myotonic contraction then continues for a variable period according to its intensity. It may last 0.1 to 45.0 seconds. If the exciting contraction is brief, the myotonia outlasts it; if long, the myotonia disappears before the contraction is over, and then is more difficult to elicit again for many seconds or minutes. Myotonia cannot be elicited by one impulse but requires three to fifty impulses to provoke it.[47] The stronger the exciting contraction (i.e., the greater the amount of muscle thrown into activity), the greater the amount of myotonia that is evoked, but the myotonia always involves less of the muscle than the contraction that elicited it. These characteristics indicate a sensitivity of muscle fibers to some by-product or metabolite of muscular contraction; so that as soon as an adequate number of impulses reach an area of muscle, a few of the fibers begin a spontaneous independent contraction which continues for a time whether or not nerve impulses continue to arrive. This response soon fatigues with repetition, even if the circulation is occluded, so that the by-product must be neutralized or destroyed by continued contraction. The duration of the spasms is shortened by giving the patient quinine but they are not usually abolished. It is still present after direct stimulation of the muscle after curarization[46]

and therefore must be produced at some point beyond that blocked by curare. Injection of acetylcholine or potassium produces myotonia but only in concentrations which normally cause some contraction, and therefore may act as other types of contraction.[47] The essential chemical mediator is unknown, although a number of chemical substances produce a reiterative discharge of the muscle fiber which is not quite identical, in that there is repetition after one impulse.[48] The anticholinesterases produce a fasciculation which does not resemble myotonia. The ease with which prostigmin in quite small dosage produces intense fasciculation in myotonic patients strongly suggests that some factor is making cholinesterase activity inefficient at the beginning of neuromuscular transmission. The myotonic rhythm in any one muscle fiber is not affected by the arrival of further impulses. Myotonia increases only by the involvement of more of the muscle fibers in the reaction. This is not explicable in terms of known properties of the end-plate.

No difference has been found between the myotonia of Thomsen's disease and that of dystrophia myotonica, except that it is less generalized in the latter disease. There is no direct relationship between the phenomenon of myotonia and the dystrophic process. Myotonic dystrophy may run its course in some members of affected families without the appearance of myotonia.[49] In some muscles, especially the tongue, myotonia may be intense throughout the disease, without the appearance of dystrophy. In dystrophic muscles there is histologic evidence that the myofibrils in some of the muscle fibers are torn and damaged by the presence of myotonia.[7] In Thomsen's disease this does not occur. Instead, the muscles are remarkably hypertrophied. This hypertrophy is probably physiologic in view of the large excess of contraction to which the muscle fibers are subjected over many years. At times all the muscles of a limb or even the whole body may be thrown into spasm. Such spasms are probably reflex in nature, for they are associated with unit action potentials and occur suddenly in muscles not previously innervated.[50] Myotonia in muscle spindles is a possible source of such reflex effects, which we have called "after-spasm" to distinguish them from peripheral myotonia.

Patients suffering from myotonia frequently complain that their symptoms are worse in cold weather. Cooling the limb does not make any difference to myotonia, however, although it slows the onset of contraction.[51] We have also found subjective worsening in cold weather to be a prominent feature in a family suffering from peroneal muscular atrophy. We would agree with Thomasen[49] that there is no basis for the separate recognition of paramyotonia, a condition in which myotonia appears only with cooling.

In some cases of hypothyroidism there is a slowness of relaxation (Hoffmann's syndrome) which is relieved by administration of thyroid extract. There is no myotonia to percussion and the electromyogram and histology are normal. The nature of the delay in relaxation is unknown, but there is some evidence that it is primarily central, i.e., an alteration of reflexes. In one case we found no electromyographic change.

DAMAGE TO NERVE ROOTS

Compression of a nerve root by tumor, collapsed vertebra or protruded intervertebral disc, besides causing root or girdle pains leads to weakness of the muscles which derive innervation from it. This weakness may not be obvious owing to overlap of innervation. Commonly, clinical inspection reveals the presence of a mild sustained spasm of these muscles even in resting posture. More often it is found only by EMG examination, in the form of regular rhythmical discharge of motor units of normal size and shape, almost continuously present. These will be present in the hamstrings for example in most L4-5 prolapsed disc patients. In vertebral lesions and spinal tumor these spontaneous potentials may be useful in indicating the segmental level of compression.[53] They are increased by any maneuver which causes root pain, and are probably a sensitive reflex indication of root damage of the same kind that in greater degree causes limitation of straight-leg-raising in L4 and L5 root lesions.

In addition the motor fibers of a nerve root have another kind of reaction to compression that is not shared with the distal parts of the nerves. This reaction takes the form of a change in excitability such that a single impulse reaching the affected region of motor root becomes transformed into a burst or group of impulses. The effect is most obvious under conditions in which nerve impulses are infrequent, and disappears with strong contraction. Thus in contracting in some weakly sustained posture the

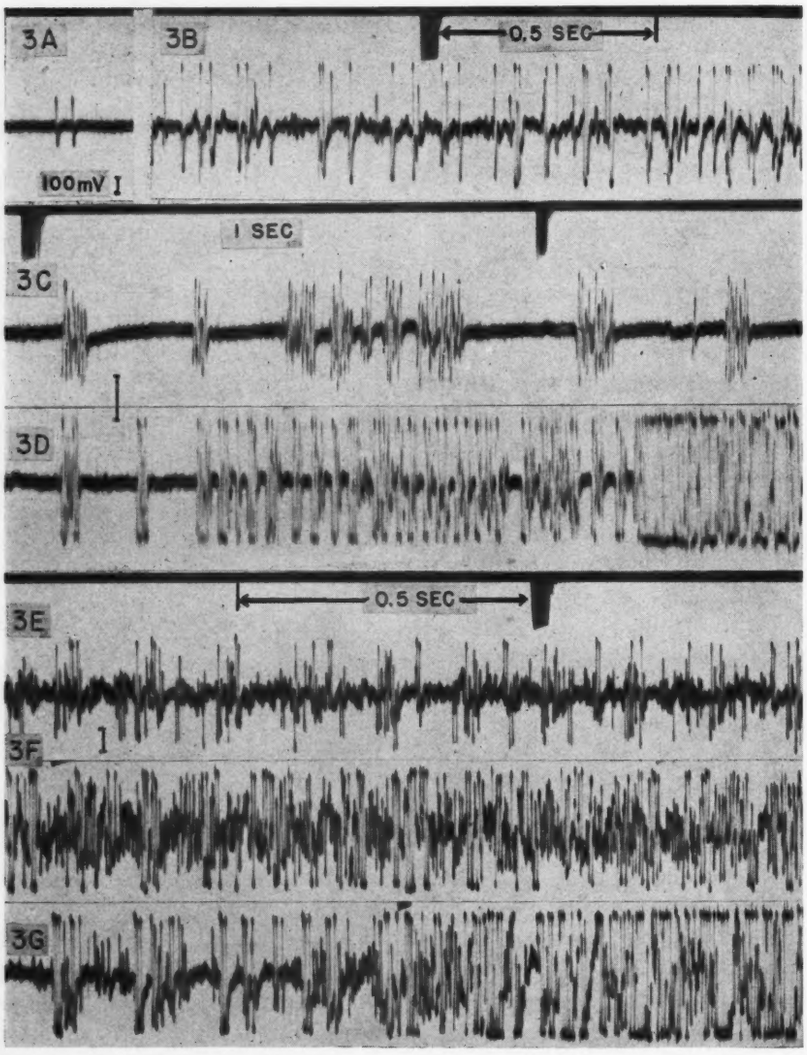

FIG. 3. A, electromyogram of a spontaneous fascicular twitch in a patient with nerve root disorder from cervical disc. B, voluntary contraction in the same muscle showing reduplicated potentials in the last half of the trace. C, spontaneous bursts of postparalytic facial spasm. D, the effect of voluntary contraction of the same muscle performed slowly. E, typical parathyroid tetany, dorsal interosseus muscle, just after the beginning of overbreathing. F, during the resulting spasm of tetany. G, effect of a voluntary contraction of the same muscle one minute after subsidence of a positive Trousseau sign.

muscles concerned may exhibit irregular small slow undulating fasciculations, and in slightly greater activity present a restless undulation of their whole surface. This kind of fasciculation is rare in spinal root lesions although it is very distinctive when it occurs. In the electromyogram it is seen to be associated with doubled or trebled beats of action potentials, either as a doubled fascicular twitch (Fig. 3A) or for a number of beats in a willed movement. (Fig. 3B.) It is much more common in the facial muscles following damage to the facial nerve, as "postparalytic facial spasm," and also as the facial spasm accompanying eighth nerve tumors. Rarely it may be associated with damage to the intramedullary course of the seventh nerve as in multiple sclerosis. An intermittent dimpling of the chin, and closure of the palpable fissure is associated with any attempt to initiate movement or expression. Large areas of the muscle may be involved in a single burst of spasm, a phenomenon commonly attributed to regeneration of a single fiber into abnormal channels. The EMG shows intermittent bursts of discharge at high frequency.[22] These occur spontaneously in bursts of varying duration (Fig. 3C) probably provoked by movements of expression. With any willed movement each

beat of the normal rhythm of discharge becomes transformed into a burst of impulses. (Fig. 3D.) Immediate relief of the spasm and its spread to other parts of the face in many cases, without loss of power of contraction, when the damaged region of the nerve can be surgically decompressed[53] shows that it is a change in excitability of the nerve fibers in the lesion, which not only transforms one impulse into a volley, but then excites neighboring nerve fibers in the lesion and thus brings wide areas of the muscle into the spasm. Such a focus of repeated discharge can thus function as an "artificial synapse" with neighboring fibers, in the manner experimentally demonstrated by Granit et al.[54]

There appears to be some limit to the number of muscle fibers which one regenerating axis cylinder can innervate, for otherwise a few regenerated fibers after any nerve lesion could always reinnervate the whole muscle, which would then always respond as a whole every time the few fibers were activated. Facial spasm is a disorder of neural excitability and is not the result of such regeneration. Attempts to induce more abundant branching of the peripheral fibers by traumatizing paralyzed muscles have not had any convincing result.[55] Indeed, our studies of the frailty of denervated muscle[7] lead us to suspect that after two months of denervation such a procedure would lead to widespread dystrophic changes. Although massive aberrant regeneration by a few fibers is unlikely to occur, the effect of a few aberrant regenerated fibers can be demonstrated under some circumstances, as in the observation of Sargent[56] of respiratory contractions in a fasciculus of triceps after old birth injury to the brachial plexus.

SPECIAL FEATURES OF THE PROXIMAL PARTS OF THE NERVE TRUNK (TETANY)

The hyperexcitability of the peripheral nerves in tetany is the basis of the well known Chvostek, Erb and Trousseau signs of that condition. It has long been observed that the application of tourniquet or cuff to elicit Trousseau's sign is more likely to be successful in mild cases the more proximal it is applied. Lewis[57] and Kugelberg[58] have shown conclusively that the fasciculations and spasm of hyperventilation tetany take origin in the most proximal parts of the nerve trunks of the arm. When the circulation was excluded from this area, the motor phenomena of tetany following hyperventilation were absent or very late in occurring compared with the nerves in the other limb with intact circulation. In parathyroid tetany the threshold of excitation of the nerve was found to fall steadily in the more proximal parts of the nerves. This is Erb's sign. The degree of fall of threshold measured as rheobase, the level of blood calcium, and the latent interval before symptoms occurred were interrelated.[58] Tingling fasciculation and spasm occurred when the excitability had increased beyond a fixed point. At this level, corresponding to 5.2 mg. per 100 ml. of calcium in the blood the nerve begins discharging spontaneously. The abnormal discharge begins with the appearance of rhythmical spikes, some single but mostly double. (Fig. 3E.) The muscle at this time is seen to show fine fasciculation. As tetany develops more and more units join the discharge, each showing rhythmic repetition of two or three beats, until a confusion of reduplicated potentials results. (Fig. 3F.) The type of discharge produced by overbreathing is identical. Just before or after the development of foci a voluntary contraction of the muscle is accompanied by a discharge showing coupled or trebled beats. (Fig. 3G.) Such discharges, beginning in foci under the cuff, are also the basis of Trousseau's sign. The longest nerve fibers, those to the hand, are first affected, and the associated tingling sensation is presumed to be due to similar change in the afferent fibers. The spasm in the intrinsic muscles of the hand leads to the well known attitude of the "main d'accoucheur" with adducted thumb and cramped extended fingers, and partly flexed metacarpophalangeal joints. It indicates overaction of the muscles supplied by the ulnar nerve.

von Bonsdorff[59] devised a more sensitive test for latent tetany. A pneumatic cuff was inflated over the upper portion of the arm for ten minutes. It was then removed and the patient was told to hyperventilate. In the previously ischemic arm tetany then developed before the other arm. Kugelberg[58] showed that in this test the foci of abnormal impulses was also in the stretch of nerve previously rendered ischemic, and that the proximal parts of the nerve trunks had the lowest threshold for this abnormality.

Like Chovstek's sign the Trousseau and von Bonsdorff tests are positive in a small percentage of normal individuals selected at random. Reid[60] examined forty-one medical students and found that after release of a cuff occluding the circulation of the limb for fifteen minutes, four

students experienced fasciculations of the hand muscles and developed tetany in the hand, maximal at the third minute after release. Kugelberg[61] examined forty students and nurses in normal health and found a positive Chvostek in ten and Trousseau in one. The data on these phenomena demonstrate that the largest and longest fibers in the peripheral nerve trunks possess a more labile excitability than the distal parts of the same nerves, and that this region is particularly susceptible to the effects of hyperventilation, hypocalcemia and ischemia. In each case the response of the affected zone is the development of foci of origin of spontaneous nerve impulses which produce fasciculation and spasm.

The liability of nerve fibers to respond repetitively to a constant stimulus during hyperventilation and tetany has been quantitatively related to the index of accommodation of the nerve by Kugelberg.[61] Normally an exciting stimulus must change sufficiently rapidly in order to set up a wave of excitation. If an electric current is increased slowly enough, the nerve membrane adapts or accommodates itself to the ionic exchange. The process of accommodation deteriorates in the presence of low calcium or a shift of pH to the alkaline side.[63] As the process of accommodation deteriorates, nerve begins to respond to a constant stimulus by iterative discharge. When the process of accommodation reaches zero, the nerve begins to discharge spontaneously. Although the threshold of excitation also usually increases with increase of accommodation, and vice versa, the two are only indirectly related, and the conception of accommodation as a separate property of nerve and muscle is important for the understanding of fasciculation and tetany. Ischemia increases the rapidity of accommodation; injury lessens it. According to the ionic hypothesis of excitation, accommodation is related to a change in the permeability of the excitable membrane to sodium ions.[64] The part played by calcium is not known but possibly the pH is the operative factor. Sensory nerves have better accommodation than motor nerves, and the median and radial nerves better than the ulnar, which is therefore the most vulnerable. The facial nerve has 30 per cent better accommodation than limb nerves.[61] In parathyroid and hyperventilation tetany the accommodation of the proximal limb nerves and facial nerve drops, resulting in the appearance of foci of spontaneous repetitive impulses originating in these areas. Although no gradient of accommodation could be demonstrated in the course of any single normal limb nerve by Kugelberg, the proximal parts of the nerves are clearly more susceptible to change of accommodation.

Ischemia of a nerve normally causes a brief fall in accommodation followed by a steady rise. Release from prolonged (fifteen to thirty minutes) ischemia is followed by a precipitous fall in accommodation in the first minute and reaches a minimum between the third and tenth minute.[61] The spontaneous fasciculations or tetany observed in some normals occurred in this latter phase.[60,63,65] The foci of origin of the abnormal repetitive impulses is in the previously ischemic area and not at the periphery as Reid supposed. The basis of Trousseau's sign is the initial small fall in accommodation in the compressed segment of nerve during ischemia, which is not sufficient to set up foci in most normal individuals.

A focus, or trigger point, for spontaneous repetitive discharge of nerve impulses in tetany also has the effect of changing a normal impulse which traverses the nerve into a double or multiple impulse.[62,65] The electromyogram of a voluntary movement then shows a series of doubled or trebled beats recurring at the rhythm of neuronal discharge, and becoming a confused series as the effect increases. (Fig. 3G.) The muscle enters a tetanic cramp. We have already mentioned the repetitive grouped discharge seen in post-paralytic facial spasm (Fig. 3C and D) and nerve root compression. These latter conditions show that the liability to breakdown in accommodation peculiar to the proximal parts of the limb nerves is shared by the nerve roots. There are, however, some obvious points of difference. The reduplication of action potential accompanying tetany has a very uniform pattern, being a pair of almost identical potentials, at an interval of 50–75 ms. (Fig. 3E), or a triplet (Fig. 3G) at slightly smaller time intervals, the last impulse being slightly delayed and larger. In facial spasm the bursts are more complex and appear to be singles, doubles or triplets of the type found in tetany complicated by a variable number of smaller and slower waves (Fig. 3C and D) which are probably derived from delayed impulses in adjacent fibers excited by the artificial synapse. In spinal root lesions we have seen only loosely coupled beats at intervals of 100–200 ms. in fascicular twitching,

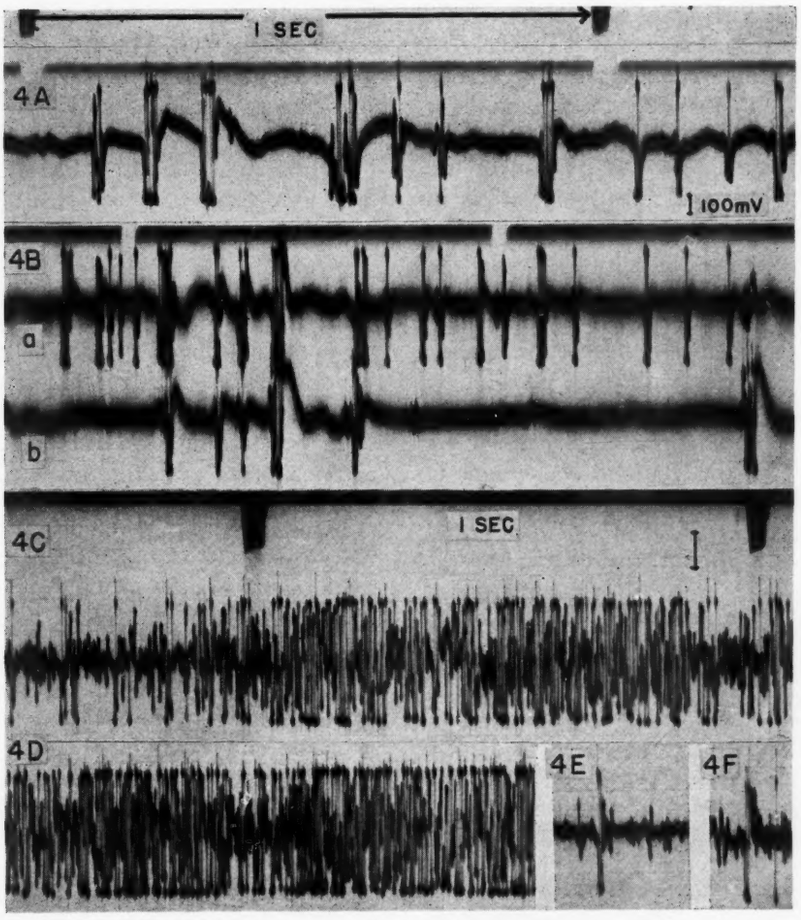

FIG. 4. A, dorsal interosseus muscle during the coarse twitches of "uremic tetany." B, the upper tracing *a* is a continuation of (A) some minutes later showing similar twitches, some of which appear also in tracing *b* which is recording from a deep flexor in the forearm. C, a small spontaneous cramp in the pretibial muscles during a weak voluntary contraction from a patient who was in normal health, with long history of liability to muscle cramps. The cramp begins with high frequency bursts in the second third of the record. D, the same at the height of a severe cramp. E and F, spontaneous fascicular twitches in the same muscle.

although doubled and tripled beats arise during contraction. (Fig. 3B.)

The coarse muscular twitchings associated with uremia present a special problem. These may affect any group of muscles and are sufficiently coarse to cause fluttering movements of the face, fingers, forearm and even proximal parts of the limbs. A puzzling feature visible at the bedside is that sometimes a single twitch seems to actuate not only the greater part of a muscle but several muscles. The condition is commonly associated with latent tetany and is considered an aspect of it, but there may be no significant disturbance of serum calcium or bicarbonate. Electromyographic recording of these twitches in several muscles concurrently reveals that they are fundamentally composed of the single, double and trebled beats of large units (Fig. 4A), sometimes with two trebles loosely coupled to form a series of six. They also commonly present appendages in the form of a reduplicated beat in another unit or group of units in the same muscle. In addition, some of the beats are associated with slightly delayed or preceding beats in nearby muscles (Fig. 4B), showing that the foci, although independent, can at times activate related nerve fibers by an artificial synapse. Since the condition is rapidly reversible, it must mean a disturbance of electrolytes such as to lead not only to breakdown of accommodation but also to the formation of an artificial synapse due to increased permeability of juxtaposed nerve fibers. The pattern of spread in the limbs indicates the nerve roots as the situation of the "chemical lesion."

The factors which make the proximal parts

of the seventh nerve liable to breakdown of accommodation are unknown. It is unlikely to be any peculiarity in vascular supply, or even its long course in a constricted long canal, for acoustic neuromas, or basilar aneurysm, both of which stretch the meningeal portion of the nerve, or even a patch of multiple sclerosis in the brain stem, will cause typical facial spasm. Since we first described the characteristic long high frequency bursts of discharge of facial spasm[22] we have been impressed by their liability to be triggered by natural impulses descending the nerve, and the physiologic similarity between this process and that which must underlie the trigger mechanism of tic douloureux. Indeed, the frequent occurrence of facial spasm, tic douloureux, and Ménières syndrome in patients suffering from cranial Paget's disease indicates that mild constrictive foraminal lesions affect the fifth, seventh and eighth nerves in the same manner. The study of tetany has shown that the process of accommodation in sensory nerves is more vulnerable than that of motor. It is noteworthy that the other known causes of trigeminal neuralgia, Ménières syndrome and glossopharyngeal neuralgia are also all lesions leading to mild constriction or stretching of the corresponding cranial nerves.

SPECIAL FEATURES OF THE DISTAL PORTIONS OF NERVE TRUNKS (MUSCLE CRAMPS)

Muscular cramps are one of the most commonly experienced neuromuscular disorders. In distinction from tetany they usually affect only one muscle group, with a special predilection for the distal muscles in the limbs, are seldom symmetrical and are relieved by contraction of the muscle. They cannot be precipitated with regularity by occlusion of the circulation to the limb, or by pressure on the motor nerve, but they also begin with fascicular twitching of the muscle which is enhanced by some mild movement of the muscle concerned. Electromyographic recording reveals that during a cramp there are periodic high frequency bursts of discharge of high voltage which begin in one area of the muscle concerned and spread to involve one and then another area[65] until the whole muscle may be presenting irregular rhythmical bursts. (Fig. 4C and D.) The frequency and intensity of discharge is much higher than in tetany. The activity begins in one focus within the susceptible muscle. This region presents irregular fascicular twitches in the interval between attacks of cramp. There may be several such foci. The twitches produce either slow indentations of the surface of the muscle or single flicks of a fasciculus, irregularly repeated at the same place.[65] The electromyogram of such twitches show considerable change in shape from one spike to another, although a general resemblance and relation to the recording electrode identifies at least some of the same muscle fibers taking part in each such twitch. (Fig. 4E and F.) Most commonly there is a small series of action potentials of diminishing size which we call a "decremental series" to distinguish them from a series of repetition of the same potential as seen in tetany. These twitches are not larger than the largest motor units, but it is not possible to exclude the possibility that two or more units are involved. The differences in shape of successive spikes indicates that a variable extent of the terminal arborization of a nerve fiber is involved in the focus. The fasciculations may be obvious when cramps are few, or vice versa. Some patients may observe such "benign" fasciculations of identical kind for years on end, often involving the small muscles of the feet and hands, with few episodes of cramps. The foci of abnormal impulses is in the muscular nerves, for their pattern is identical with that of the fasciculation produced by large doses of prostigmin, which experimentally can be shown to set up abnormal impulses in the terminal arborizations of the nerves. Yet there is no certain evidence at present as to the nature of such foci. Such cramps and fasciculations are not induced by hyperventilation, or by cuff tests or by von Bonsdorff's test.[65] It is possible that they may represent simple mechanical irritation or ischemia of the smaller intramuscular nerve bundles. These are normally protected from compression by muscle fibers by the slender sheath of Henle, separated from the nerve fibers by a fluid of unknown composition and origin.

The best known association of such peripheral cramps is with loss of sodium, either from profuse sweating, diarrhea or diuresis, but the actual change in the muscle and nerve is unknown. They also occur in those with large muscles particularly in former athletes, when no loss of sodium can be demonstrated and no relief is afforded by ingestion of sodium chloride. The muscles most frequently involved are the calf muscles and the small muscles of the feet. When fully developed such cramps have the same clinical appearance as the carpopedal spasm

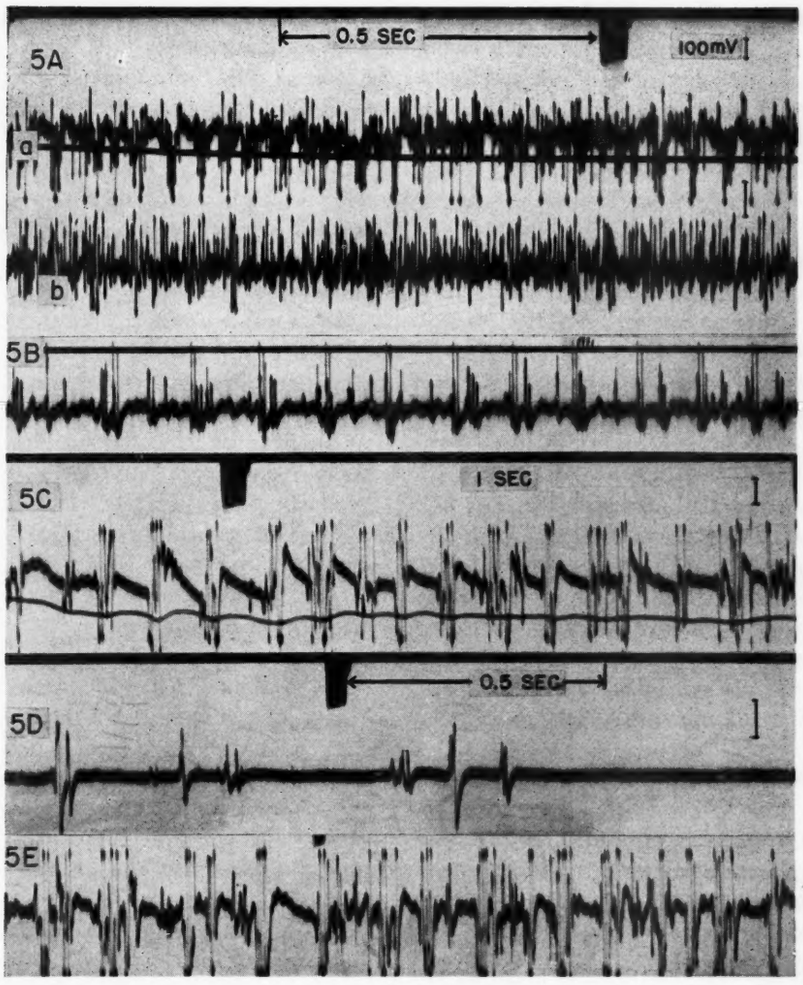

FIG. 5. A, painful cramp of the forearm and hand induced by inflating a cuff on the upper arm in a young man whose complaint was of spontaneous cramps in the calf muscles. The upper electromyogram *a* is from the forearm flexors, the lower *b* from dorsal interosseus. There was no history of tetany in the upper limbs; familial large muscles. B, from interosseous muscle of the same patient during cuff test. C, a weak voluntary movement in the adductor pollicis muscle of a patient recovering from diphtheritic polyneuropathy. D, spontaneous fasciculation. E, voluntary contraction of pretibial muscle in the recovery stage of acute alcoholic wrist-drop and foot-drop.

of parathyroid tetany. In a young man with large muscles, who had suffered from severe cramps for three years for no obvious reason, and who had been formerly very athletic, electromyographic record of a cramp showed a mixture of discharges of peripheral type with those of tetany. (Fig. 5A.) A cuff test showed a mild positive reaction for tetany after release of the cuff. (Fig. 5B.) We conclude that the abnormal foci were not entirely peripheral in his case. Indeed, in some types of tetany, particularly those associated with diarrhea, there is evidence that the type of muscle cramp is identical with common peripheral cramps beginning in the calves of the legs. In this kind of tetany there is considerable doubt as to the nature of the ionic disturbance. Thus in two cases reported by Engel et al.[66] with chronic diarrhea, low serum calcium was not associated with tetany because of a concomitant hypokalemia. When potassium chloride was given tetany with severe cramps in the legs appeared, and could be abolished by administering calcium salts, or by allowing the serum potassium to return to its previous low level. The sodium level remained within normal limits. Conversely hypokalemia arising in the course of chronic nephritis, or of treatment of diabetic coma and a wide variety of other conditions, may be associated with either coarse muscular twitching, tetany and peripheral muscle cramps or all three. The toxin of the "black widow" spider

of the species *Latrodectus* produces muscular cramps which appear to be of the peripheral type yet are relieved by calcium gluconate.[67] Magnesium deficiency may lead to spasms clinically indistinguishable from tetany[68] with normal serum calcium, and not relieved by injections of calcium salts. Chvostek's sign presents features of both the proximal and peripheral types of hyperexcitability of nerve and is non-specific in this sense. Its frequency in a high proportion of normal individuals, 29 per cent according to Graham and Anderson,[69] therefore reflects the result of minimal changes of all types.

Therefore, although two main types of spontaneous peripheral spasm and associated fasciculation can be distinguished by the cuff test, and indicate at least two types of disturbance of polarization of the excitable membrane of peripheral nerve, there is no good evidence as to the essential ionic disorder. Until more detailed studies of the changes in electrolytes are available we can state only that low calcium favors a proximal focus and low sodium a peripheral.

NEUROPATHY

The flaccid paralysis of peripheral neuropathy with associated glove-and-stocking sensory loss is also a condition that is clear enough when severe but which may present doubtful types of weakness and paralysis when mild or when radicular in type. In severe forms muscle biopsy shows scattered small groups of muscle fibers undergoing denervation atrophy, but the appearance is distinctive only when the duration has been many weeks or months. Different groups of muscle fibers are then seen in different stages of atrophy and degeneration.[7] Each nerve fiber normally innervates a group of twenty to fifty muscle fibers ("motor unit"). The presence of different stages of degeneration in groups of muscle fibers of similar size implies serial damage to the related nerve fibers. Paralysis of less than two weeks' duration may be severe without any histologic change in the muscles.

The electromyogram of a paralyzed muscle may show no action potentials of any kind. Fibrillation if present is usually less than after nerve section. This is because in mild to moderate degrees of most kinds of peripheral neuropathy a number of motor nerve fibers suffer from block of conduction without anatomic degeneration, in the form of loss of myelin over stretches of axis cylinder, with normal myelin above and below. This type of partial nerve lesion is the "periaxial segmental neuritis" of Gombault[70] and has been found in alcoholic and lead neuropathy,[71] beri-beri[72] and porphyric neuropathy.[73] We have observed it in the nerve roots in diphtheritic neuritis. In these conditions there is often a mixture of complete Wallerian degeneration of some nerve fibers, with partial lesion of others.

In studies of experimental compression lesions of nerve, Denny-Brown and Brenner[5] found that partial lesions in the form of a nerve block lasting for periods up to nineteen days could be produced in zones of transient ischemia. Such a lesion is common in tourniquet paralysis and pressure palsy. The lesion is essentially loss of myelin for a variable distance, with preservation of axis cylinder and resumption of myelin distal to the lesion. The beginning of the lesion is a dissolution of the myelin sheath for a short distance (0.01 to 0.04 mm.) on one side of each node of Ranvier in the damaged region in the course of the second day after a sufficient duration of transient compression. All the nerve fibers in the previously compressed area showed this change at the nodes of Ranvier. The extent of damage was related to the duration of complete ischemia in the compressed area. More prolonged ischemia resulted in demyelination of a greater length of the myelin segment, so that the remaining myelin covered as little as a quarter of the normal segmental length of 1 mm. Greater damage than this resulted in necrosis of the axis cylinder, with resulting Wallerian degeneration beyond the point of interruption. In partial lesions of this kind restitution of a thin lipoid layer over the bare region of axis cylinder was observed to begin between the tenth and nineteenth day. Conduction then returned abruptly. The ultimate completion of a normal myelin covering for the previously naked regions requires two to three months in the cat. The block of conduction was predominantly motor although all types of nerve fiber at the level of previous ischemia were similarly affected. This type of partial lesion could also be produced by cooling below 8°C.[74]

In pressure palsy Erb showed that it may be possible to demonstrate by faradic electrical stimulus that the nerve is excitable below the point of damage although muscular contraction is not caused by stimulation above this. In

polyneuropathy the regions of block are scattered and commonly in nerve roots and plexus, and not electrically demonstrable, although the ease of electrical stimulation of the distal parts is often inconsistent with the patient's inability to contract the same muscles.

The process of conduction of the nerve impulse involves the progressive depolarization and repolarization of the membrane of the axis cylinder with the same electrical characteristics of conduction of the wave of excitation in muscle.[76] In the case of vertebrate motor nerve fibers, however, the process is complicated by the presence of the myelin sheath. This sheath is in the form of segments of myelin about 1 mm. in length for fibers of average size, each separated from the next by the cementing substance of the node of Ranvier. Huxley and Stämpfli[75,76] by a series of brilliant experiments have demonstrated that the electrical potential accompanying the propagated impulse in medullated nerve leaps from one node of Ranvier to the next ("saltatory conduction"). There is evidence that the ionic interchange also takes place only at the node of Ranvier. The amount of inward flux of sodium at the node of Ranvier with each nerve action potential must be extremely small[16] but propogation is effectively blocked by replacement of external sodium. We have as yet no knowledge of the nature of the disturbance of polarization at the node of Ranvier in the partial ischemic nerve lesion, or the similar lesion produced by other agents such as lead or thiamin deficiency, although the associated block of conduction clearly indicates a breakdown of the "sodium pump." The affected area of axis cylinder stains poorly with silver impregnation, and strongly with basophil stains, indicating a change in chemical affinities.[5]

In the phase of recovery from peripheral neuropathy some motor units in the electromyogram may be seen discharging at rates of only one to two a second, however intense the effort. These are probably the result of a recovering partial segmental nerve block, which still will not transmit the full discharge rate. At a later stage of recovery reduplication of action potentials becomes prominent for a time. We have observed this in diphtheritic polyneuropathy when fascicular twitches and reduplicated rhythm typical of partial root lesions may dominate the electromyogram (Fig. 5C), and in recovery from acute alcoholic polyneuropathy of the beri-beri type. (Fig. 5D and E.) In the latter case the decremental repetitive discharge indicates distal foci near the end-plates, with minor muscle cramps during voluntary contraction. (Fig. 5E.) The associated extreme tenderness of the muscles is then additional evidence of the distal situation of the neural damage. Associated fasciculation was of the peripheral "decrementing" type. (Fig. 5D.) This disturbance appears to us to be the basis for the "myotonia" and muscular hypertrophy described by others as post-neuritic manifestations.[77–79] It is not present following regeneration of complete lesions. These findings in the more rapidly reversible partial lesions of nerve indicate that the temporary changes associated with muscle cramps and tetany also probably take place at the node of Ranvier. In addition, they indicate that the vulnerable mechanism in peripheral nerve is not that which produces polarization, but that which maintains it in the face of all chemical and electrical tissue changes except those associated with the propagation of a nerve impulse.

The electromyogram of incompletely paralyzed muscles in chronic peripheral neuropathy presents an additional unusual feature which does not appear to be related to the type of nerve lesion. The only motor units that can be activated may be very large ones, sufficient to cause a visible tremulous contraction in one part of the muscle with large rhythmical action potentials. We call this "contraction fasciculation" for it appears only with use of the muscle.[22] The electrical potential may be six or eight times the voltage of those units that normally begin a muscular contraction and it is polyphasic. Such units may possibly result from abnormal regeneration, but their presence immediately after spinal anesthesia or soon after partial traumatic nerve injury indicates that they are normal large motor units, normally active only in strong contractions, and now left "uncovered" by the absence of activity in the many small units which normally begin a muscular effort.

MOTOR NEURONE DISEASE

Twitching of muscles is a cardinal sign of motor neurone disease (progressive muscular atrophy, amyotrophic lateral sclerosis). The twitches are repeated in identical form only at intervals in any bundle of muscle fibers and can be individually recognized by their single action potential, which usually has the size and shape

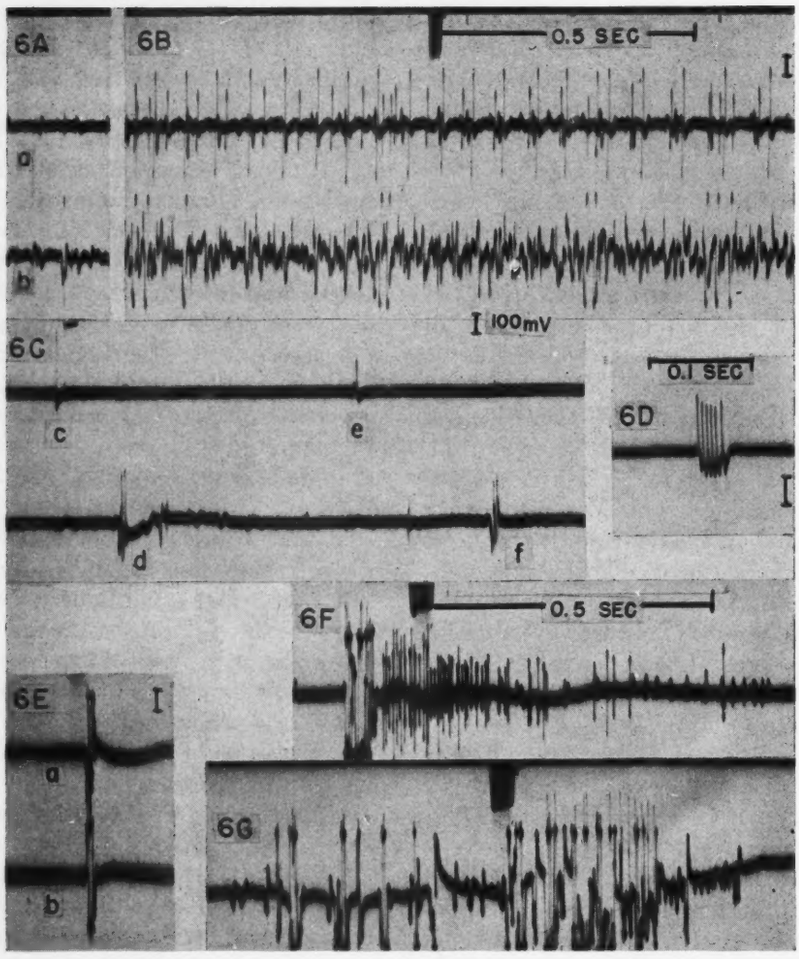

FIG. 6. A, progressive muscular atrophy, upper tracing *a* from biceps muscle, lower *b* from medial part of same muscle. A twitch of fasciculation is seen in *b*. B, voluntary contraction of the same muscle with many units discharging normally. The unit seen in (A) at first discharged rhythmically at fifteen beats a second, but at the beginning of (B) began a stammering type of reduplicated discharge, although the patient's effort was well sustained. C, several types of spontaneous fasciculation in the same muscle; *c* and *e* are of unit (central) type, *d* peripheral and *f* proximal. D, one of a series of bursts of true myokymia in dorsal interosseus muscle in a student aged thirty-one years who had noticed occasional fluctuations of various limb and body muscles for seven years. E, *a* from distal part, *b* from proximal part of a flexor muscle of the foot, from woman aged fifty-eight who had had irregular coarse twitching of face and limb muscles for eight years. In (E) a small twitch shows a burst of potentials at high frequency in *b*, with slower repetition in *a*. Other types of twitching in lead *a* are seen in (F) and (G). These were associated with only a very brief response in lead *b*.

of a motor unit. When we originally differentiated these twitches from fibrillation,[22] we noted that the same unit could discharge normally in muscular contractions although the occurrence of the spontaneous discharges indicates an active disease process, which neuropathology demonstrates to end in destruction of the motor neurone. We therefore postulated a disorder of central neuronal excitability as their cause. Subsequently others have shown by nerve block[80] and by nerve section[81] that some fasciculation will then still occur, and postulated a peripheral origin for the abnormal impulses. Our later experience[82] indicated that the fasciculation after nerve block was not as intense as before, indicating both central and peripheral origin for the disturbance. If the electrical records of fasciculation in this disease are examined in terms of the features we have outlined above, it is clear that several types of fasciculation occur in motor neurone disease. The decrementing type of peripheral response, a large wave followed by an irregular series of smaller appendages, typical of prostigmin fasciculation, is an uncommon type. Two identical large unit potentials, at an interval

of 0.1 to 0.5 second, repeated again after two to thirty seconds are frequently seen, and a rapid couplet with intervals of 0.02 to 0.05 second is less common. All these are characteristic of fasciculation taking origin in peripheral nerves, typifying distal, intermediate and proximal foci. In addition the type of large single unit potential we originally described, repeated singly in identical form only at very long intervals of one to five minutes is the commonest type of twitch seen in an active phase of motor neurone disease. (Fig. 6A.) When a willed innervation of the muscle shows that the same neurone has a halting irregular paired discharge, even with maximal effort, as in the lower tracing in Figure 6B, it is clear that this type of discharge comes from a disordered nerve cell. The irregular, reduplicated rhythm betrays disturbance of the "pacemaker." We therefore believe that motor neurone disease is primarily manifest as a breakdown of the excitability of the neurone membrane, axon as well as synaptic area, indicating a diffuse metabolic disorder of the membrane permeability.

BENIGN FASCICULATION AND MUSCLE HYPERTROPHY

In the preceding sections various forms of disorder of the excitability of nerves have been discussed. The associated disturbances take origin from trigger points which may be determined by disturbance of electrolytes, by ischemia, or by partial anatomic lesions in the form of recovering segmental demyelination. Electromyographic study reveals differences in the type of abnormal discharge which are determined more by whether the trigger point is proximal or distal in the nerve trunk than by the nature of the exciting cause. The disturbance is more clearly revealed by the distribution of the spasms and the presence or absence of muscular atrophy and weakness. The continuation of muscular fasciculation for long periods of time, without atrophy, and with few cramps or spasms, presents a special problem. Such "benign fasciculation" is usually identical with that which is associated with simple muscle cramps of the peripheral type, with variable decrementing type of electrical potential.[65] The electromyogram of voluntary movement then shows occasional small high frequency "larval" cramp discharges in the muscles, which do not develop into a cramp that is obvious to the patient. Some of these subjects have a weakly positive cuff test, presenting doubled unit discharges, but without obvious tetany. It is presumed that it is due to some mild unknown disorder of permeability. It is of interest that this phenomenon may be present for many years and the calf and forearm muscles are then greatly enlarged. One such patient informed us that the huge calf muscles were present in several members of his family. As in congenital myotonia, the hypertrophy of muscles in such cases appears to be determined by the inborn abnormality of innervation, and we believe that this is the cause of "hypertrophia musculorum vera."

In three patients, two of whom we have already reported elsewhere[65] we have found true "myokymia" as described by Kny[83] in the nature of an undulating, slow fascicular twitching which appeared in various parts of the limbs, abdomen and back for a period of years without obvious cause and with no recent history of muscle cramps. The electromyogram is very distinctive, showing groups or trains of 2 to over 200 unit potentials of identical size, at the rate of approximately 50 a second, thus producing little tetanic contractions in the muscles. (Fig. 6D.) The smaller groups of two and three are identical with the discharges of tetany, and are greatly intensified by the von Bonsdorff test although typical tetany is difficult to produce in these patients. The condition is improved, but not relieved by oral administration of calcium. In another patient, a woman of fifty-eight, a condition of coarse muscular twitching resembling that seen in uremia and presenting identical periodic bursts in the limbs, trunk and right side of the face had been present for seven years. It had been called "chorea." She had suffered severely from cramps in the fingers and toes with three earlier pregnancies. The condition was only slightly improved by oral calcium. She appeared in perfect health. Electrolyte studies were unfortunately not available. An electromyogram showed discharges of proximal type propagating to neighboring nerve fibers at times. (Fig. 6E.) At other times the action potentials showed complex propagation to neighboring fibers (Fig. 6F) or the stammering discharge of uremic type of tetany. (Fig. 6G.) In the absence of spontaneous or induced tetany the term "latent tetany" would appear incorrect, although we must assume that some undefined disorder of

ionic permeability in the proximal nerve trunks is present.

CONTRACTURE

Although the pharmacologist confines the use of the word contracture to types of muscle contraction without action potentials, for example, that produced by a large dose of acetylcholine, the clinician uses the term in a totally different sense. In the clinic contracture is defined as a limitation of movement at a joint traceable to a fixed shortening of the fully relaxed muscles. There is no evidence that such shortening of a muscle is due to a change in the neuromuscular mechanism. We believe it is related to changes in the collagen and reticulin of the muscle and tendon,[7] and its occurrence in Addison's disease and related endocrine disorders may indicate that it is due to changes in electrolytes as Thorne[84] suggests. Such changes are beyond the scope of the present topic. We may comment only that the absence of contracture in denervated muscle is probably due to the alterations in the connective tissues of muscle which follow denervation and which we mentioned in the first section.

CONCLUSION

Diseases primarily affecting the contractility of muscles such as muscular dystrophy or the more destructive types of myositis do so in virtue of the loss of myofibrils in the muscle fiber. There is loss of contractility without change in excitability. Besides loss of muscle bulk and power of contraction the altered physiology is revealed only by diminishing size of motor unit potentials in the electromyogram and loss of individual muscle fibers in biopsy section. Degeneration of myofibrils as a result of trauma is the most certain method of demonstration of the primary fault.

The excitability of muscles is affected chiefly by large changes in body electrolytes, particularly in ionized potassium and sodium as in periodic paralysis, hyperkalemia and Addison's disease. A fall in available intracellular potassium, a rise of extracellular potassium or a fall in extracellular sodium appear to be the significant factors. Block of the end-plate mechanism of the neuromuscular junction by myasthenia gravis indicates the presence of some curare-like substance produced by the arrival of nerve impulses at the end-plate. The phenomenon of myotonia indicates the opposite effect of some by-product of muscular excitation in stimulating local contractions in muscle fibers.

The effect of diseases of peripheral nerves is to damage the node of Ranvier of the myelin sheath, setting up an abnormal permeability in that situation which blocks the saltatory conduction characteristic of myelinated nerve. Lesser degree of disturbance results in repetitive transformations of single nerve impulses as they pass the point of damage, and the production of spontaneous repetitive discharges owing to loss of power of accommodation. This indicates that polarization is not at fault, but that it is maintained with difficulty in the presence of electrical and chemical changes that would not otherwise be adequate to set up an impulse. The form of such abnormal repetitive nerve impulses differs according to whether the foci are in the proximal, intermediate or distal parts of the nerve trunk. These differences determine the clinical features of such disorders as muscle cramps, tetany, nerve root fasciculation and myokymia. Coarse twitching and facial spasm arises from breakdown in the electrical insulation of nerve fibers in association with loss of accommodation, from similar disturbances of the node of Ranvier in proximal nerve trunks and roots. The variety of circumstances under which such foci can arise is discussed. Associated muscular hypertrophy is considered to be physiologic. More exact measurement of the excitability of nerve, end-organ and muscle fiber in the intact human, with better methods of assessment of the ionic polarization of excitable membranes, are necessary for better understanding of a variety of common disorders of muscle and nerve.

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Clinic on Psychosomatic Problems

A Case of Low Back and Leg Pain Complicated by Psychologic Factors

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric Services of the Massachusetts General Hospital. This psychiatric conference was edited by Drs. Stanley Cobb and John C. Nemiah.

THE psychiatric conference to be reported here deals with the problem of a man totally incapacitated following an injury which resulted in back and right leg pain. This was apparently caused by a known spondylolisthesis and scarring around the first sacral root on the right. He had not worked for over three years, had been in a general hospital for all but three weeks of the year prior to admission, and had been taking 900 to 1,200 mg. of demerol daily for six months. Cordotomy, electric shock treatment and lobotomy had all been recommended for him, and he was referred to the hospital for psychiatric evaluation to decide if any of the procedures was advisable.

CASE PRESENTATION

DR. JOHN C. NEMIAH: The patient, forty-nine years of age, was a contractor. A little more than three years before his admission, while lifting a heavy plank, he felt a sudden severe pain in his low back which in a few hours radiated down the lateral aspect of his right leg into his little toe. He remained home without relief of symptoms for three months and then underwent a spinal fusion for what was diagnosed by x-ray as spondylolisthesis at L5-S1. His recovery was complicated by pulmonary emboli, and for some months after this he was in and out of the hospital attempting to get relief from his ever present pain which had not been helped by surgery. A year later he was first admitted to this hospital. Examination at that time showed less than 50 per cent motion of the spine, straight leg raising of 40 degrees on the right and 60 on the left and a diminished left ankle jerk and hyperthesia along the lateral border of the right foot and calf. X-ray was interpreted as showing a fusion at L5-S1, an old spondylolisthesis at L5-S1 with forward displacement of the body, and a lateral wedge deformity of L5. The second lumbar intervertebral disc space was narrowed. During a second admission a month later the patient was re-explored, at which time the fusion was found to be solid; however, considerable scar tissue was seen involving the right sacral root, which was freed. The patient had somewhat less pain following this procedure but was unable to work, and by a year before admission he had begun to demand demerol fairly regularly. Three admissions to the hospital failed to bring him lasting relief, and the patient became increasingly anxious, discouraged and depressed. Following an abortive suicidal attempt by swallowing barbiturates, a cordotomy was advised but this the patient refused. After another year of invalidism during which he spent all but three weeks lying in a local hospital receiving demerol in an attempt to control his pain, he was readmitted to this hospital for the purpose of evaluating the advisability of electric shock treatment, lobotomy or cordotomy.

Family history: Both the patient's parents were dead. He gave little information about his mother, but his few remarks about her indicated a somewhat domineering person, toward whom the patient had always been close. The patient had very mixed feeling about his father, a doctor. He praised him for his skill as a physician, but resented the fact that as a youngster he rarely saw his father and that in his contacts with him he had always found his father rigid, stern and strict. From the age of twelve on he had tried to be financially independent of his father, at least as far as spending money was concerned. He had five siblings, three older sisters and a younger brother and sister, all of whom were college graduates.

Past history: The patient's general health had been fairly good. An appendectomy at nine years followed by peritonitis kept him in bed for

six months, but his only other major illness had been septicemia at the age of twenty-three. Since his early twenties he had occasionally had mild back pain, but this had never incapacitated him. For the greater part of his adult life he had suffered from "migraine headaches"—unilateral throbbing headaches which were accompanied with nausea and relieved by sleep, usually appearing at night, over weekends, or after a siege of hard work.

Social history: The patient had almost no memory of the first dozen years of his life. The one thing he recalled with any clarity was his disappointment, when at the age of six, his parents had refused to allow him to move to California to live with a couple who wanted to adopt him. At thirteen he began a paper route to free himself of asking his father for spending money and by sixteen he was working regularly after school. At eighteen he had a serious falling out with his father. The latter, in accordance with plans that the patient would go to medical school, wanted him to attend a local institution; the patient preferred to get his training out of town, partly to escape the domination of the father. Each remained immovable in his decision, and the patient solved the dilemma by going to work for a building contractor, which was what he wanted to do in the first place.

At twenty-three years of age he married after a brief courtship during which he would frequently feel lonesome and vomit after leaving his fiancée. A year after this when his wages were cut as a result of the depression, he decided to go into business for himself. With a partner he established a contracting company which grew rapidly and successfully, largely owing to his own efforts. The patient described himself as being "too perfectionistic," and a hard man to work for. It was difficult for him to delegate authority and as a result he spent a great deal of time working himself and closely supervising the work of his employees to make sure that the job done for his customers was perfect. A year and a half before his injury the patient formed a real estate company in addition to the contracting concern. Although his major interest and enthusiasm was in the building end of the business, he felt that his partner was too passive to be a salesman, and accordingly against his deepest inclinations he took over the job of selling. By hard work he became very successful at this but found, although nominally no longer connected with the actual building of houses, he was still impelled to supervise the construction work as well as selling. As a result for a year before his injury he was working seven days a week, twelve to sixteen hours a day. He enjoyed the work but would occasionally wonder whether "it was worth all the trouble," or fair to his family to be away from them day in and day out.

Physical examination: On admission the general examination was negative. Positive findings were limitation of motion in the lumbosacral spine, bilaterally absent ankle jerks and hypesthesia over the lateral aspect of the right leg and foot, including the little toe.

Laboratory studies were within normal limits.

Mental status: During the initial interview the patient was cooperative but seemed tense and ill at ease; he spoke somewhat hesitantly, in a low voice and rarely looked at the interviewer. He complained vehemently about his pain and lack of relief, and used adjectives like "agonizing" and "unbearable." Particularly striking was his hostility toward the doctors and other personnel who had cared for him in the past: he felt he had been further injured by injudicious rehabilitation after his first operation; he complained of the confused and contradictory opinions given him, and thought all his doctors were in league with one another to cover up their mistakes. He stated that the doctor had lied to him about the nature of his second operation and that he had discovered the truth only by a surreptitious look at the doctor's private notes. He was concerned that his doctor at home was "trying to get rid" of him as "too difficult a case." The patient expressed these ideas with considerable resentment and feeling, remaining, however, apparently friendly to the interviewer.

Hospital course: During his first week in the hospital the patient complained bitterly of pain, was demanding of demerol at frequent intervals and was very critical of the nursing staff when he was not given medication at once upon request. He remained friendly with the psychiatric consultant but when it was suggested to him that he be transferred to the psychiatric ward for further evaluation, the patient became suddenly intensely disturbed. He began to hyperventilate, sweat and tremble; he complained of extreme pain and stated that there was nothing emotional about his illness—his only problem was pain. He became very critical of the hospital and its staff, insisted that an operation on his back was what was required

and that no one was telling him the truth about his condition. He stated with considerable hostility that the doctors thought his pain was imaginary and that he was "mental" and he refused to be moved to a ward with "a lot of nuts." He believed the best procedure was to sign out and go to a completely new hospital for a fresh, unbiased opinion. The next morning the patient was much calmer, stated that he had decided he would get nowhere without "faith in the doctors" and agreed to transfer to the psychiatric ward.

The patient's first stay on the psychiatric service lasted three weeks. He adjusted fairly well to the ward routine, but continued to complain frequently of "being in agony" with pain, and to demand medication which was given him in amounts of from 900 to 1,200 mg. per twenty-four-hour period. On one occasion when refused medication in the middle of the night, the patient became panicky, left the ward in his pajamas and went to a telephone with the idea of calling another hospital for immediate admission where he could get the help and medication he felt he needed. The next morning he was obviously angry and acutely anxious, and showed the same behavior and complaints as on the occasion of his contemplated transfer to the psychiatric ward.

The patient was seen six days a week by the psychiatrist, eight of these contacts being hour-long interviews, oriented toward learning more about the patient's defenses, fantasies and feelings. During all of these periods the patient continued to be ill at ease. He rarely looked at the examiner, spoke frequently in a low voice and exhibited little spontaneity and animation. There were frequently long pauses and the patient rarely spoke continuously for any length of time.

During these interviews three important trends of thought were developed and elaborated upon:

(1) The patient's tremendous drive toward work and physical activity had been noted in obtaining the initial history. This the patient now related to a strong sense of responsibility to his family. The patient felt that without this sense of responsibility he would fall into an aimless, purposeless, passive type of existence. He associated directly to this a period in his life when he had almost become involved with a married woman who later "ruined" another man's life by making him completely dependent on her. The patient felt that he narrowly escaped this fate and that but for lucky circumstances "it could have happened" to him.

(2) On several occasions the patient expressed the thought that his pains were punishment for his past life. These feelings were not pursued extensively but were associated with feelings and fantasies of hostility and violence.

(3) The patient expressed extreme anxiety about undergoing a cordotomy. He stated that every operative procedure had been followed by unusual and serious complications and he was sure that cordotomy would leave him a cripple. This raised in him all his anxiety about falling into a helpless, passive type of existence. Furthermore, his fear of cordotomy led by direct association to a memory of an episode when he was sixteen, at which time his own father had removed his tonsils at home. The procedure had come as a complete surprise to the patient, who had been grabbed by his father and an assistant, forceably held down despite his struggles on the table, and smothered with an ether cone. This the patient looked upon as a brutal assault by his father, against which he had fought violently, giving his father a black eye in the process; he felt his father had handled him with extra roughness while he was under anesthesia as punishment for his resistance.

On a basis of the material obtained in these interviews it was decided to manage the patient in the following way. (1) Further exploratory interviews were to be avoided. Instead the patient was to be seen frequently but briefly, to give him encouragement and to support and strengthen his psychologic defenses of activity and independence. (2) The therapist was to behave in a relaxed, friendly, accepting and somewhat passive manner, fulfilling where possible the patient's demands, but avoiding any appearance of ordering or coercing the patient into any specific procedure or line of action. (3) The choice of cordotomy was to be left up to the patient without further advice or pressure, and he was to be allowed to decide on his own future management except insofar as his choice might be actually detrimental to his eventual recovery.

Under these circumstances the patient decided against cordotomy and elected instead to have a sciatic nerve stretching under pentothal.® The orthopedic service agreed to this, although they felt it would have no actual value from a physiologic point of view in the light of the

patient's previous reaction to two of these procedures. The patient was accordingly transferred to the orthopedic service where this maneuver was performed at the beginning of his fifth hospital week.

After this procedure the patient was seen twice daily by the psychiatrist, began active physiotherapy and worked in the occupational therapy shop where he developed an interest in wood making; he poured a tremendous amount of energy into this pursuit and spent the greater part of his free time designing patterns and working them out in wood. The first few postoperative days the patient had multiple complaints. Although the pain was no longer experienced in his foot, he complained of episodic severe pain in his back and legs, and had numerous other small complaints—sore throat, sore hemorrhoids, toothache, ringing in his ears, etc., which he constantly presented to the therapist along with his usual remarks on the stupidity of the personnel caring for him.

He continued also to require demerol, 150 mg. every three hours, and was unable to cut down the amount when this was left up to him. Accordingly, a plan was worked out with the patient whereby the psychiatrist controlled the amount of demerol given at each injection and the patient controlled the frequency of administrations, being allowed to have medication as frequently as every hour if he wished it. On this regimen in ten days' time the dosage was cut from 150 to 5 mg. an injection and the patient reduced his frequency from medication every three hours to four or five times a day. He increased his activity, complained less of pain, felt more encouraged and began to make concrete plans for moving permanently to another part of the country.

At this time, however, one night the patient was not given medication when he asked for it. He became extremely agitated, made a threatening attempt to jump out of the sixth floor window and was transferred to the psychiatric ward once more, over his strongest protests and struggles. The following morning he exhibited the angry, anxious, tearful, complaining and criticizing behavior which he had shown on previous occasions when medication had been refused him. Although he demanded to be allowed to leave the hospital where "a man could get some help for his agony," the psychiatrist accepted his behavior and complaints quietly and without comment, and by the end of the day the patient had generally regained his composure.

From this time on he appeared to improve. He engaged enthusiastically in ward activities, was generally cheerful and encouraged, and rarely complained of pain or of a lack of help and attention. Instead there was a striking change in the content of his remarks to many complaints about the general stupidity and ineptness of the ward nurses, of the planning of meals, of the carpenters and plumbers who occasionally visited the ward for repairs, of patients who worked in the occupational therapy shop with him and of everyone with whom he came in contact. In all of this the patient attempted to demonstrate how much more he knew than others. During this last phase of his hospitalization he completely discontinued his demerol and after a successful weekend trial visit home, he was discharged, two and a half months after his admission. At the time of discharge he stated that he still had pains at times, but that they really did not bother him very much and that he could handle them.

Follow-up: The patient was last heard from six weeks after discharge. At that time he had driven some 10,000 miles and had moved to Florida where he had bought a business which he felt he could operate with profit. He occasionally had pain but was no longer concerned with it. He felt he had "learned to live with it" and had thrown away all the medicines he had had at home during his attempts to obtain relief. He looked forward with confidence to his new home and business activities.

STAFF CONFERENCE

MISS DANIELS: The patient was active in the occupational therapy shop, especially in wood working. As time progressed he grew increasingly domineering, would tell the other patients how to do things and would be critical of their work. His own work, however, was not good and he was extremely sloppy in the shop and careless with tools, becoming quite destructive at times. He seemed to resent any sort of criticism and I was surprised toward the end of his stay when we finally spoke to him about his behavior that he took it gently and really tried to cooperate and be less messy.

DR. COBB: The last morning on the way out he stopped to see me. He was a little effusive, a little overactive. He was starting for Florida,

everything fine. I asked, "How about the pain?" He answered, "Oh, I have that still, but I can live with it now." He is out of his invalidism. He was a 100 per cent invalid a few months ago, worse than 100 per cent because he was spreading terror around him, to the nurses and the doctors, especially the doctors. This extreme hostility was an interesting part of it.

DR. BARRY: Considering the seriousness of the problem this represents a decided therapeutic improvement. Nobody who has not tried to take care of a series of these patients appreciates the impact of their hostility, both expressed and unexpressed. They are frequently so belligerent that they antagonize doctors, nurses and other patients, and one gets the feeling they are deliberately trying to be rejected. This man raises one point I feel is important, namely, his increasing pain, anger and anxiety, if he does not get medication for his discomfort before a certain point of intensity is reached. This occurs frequently in my experience and I try to obviate it by leaving an order for routine by-the-clock medication rather than writing a "p.r.n." order.

The diagnosis is very important in these cases, and one must distinguish between traumatic neurosis, compensation neurosis and an already existing psychoneurosis which is accentuated by injury. Compensation factors appear to be minimal in this man's case, and I believe he has most of the characteristics of a traumatic neurosis especially in that he was doing extremely well until he got hurt, at which time his psychologic defenses were shattered.

Furthermore, anyone who has had a long series of cases like these knows how difficult it is to be certain that one actually is dealing with a neurosis and not with an unrecognized lesion. In a series of fifty cases two turned out to have tumors, both of whom had initially been considered to have neurosis. The whole matter is further complicated by the fact that many of these patients do have a lesion causing pain, upon which is superimposed a massive set of psychologic symptoms and emotional reactions.

Treatment is very difficult and this patient represents an excellent therapeutic result. I think we can be misled, however, into thinking that all patients will recover so rapidly. I have seen several with results comparable to this one, but most of them required years of psychotherapy before relief of symptoms occurred.

DR. COBB: Do you consider this man unusually hostile?

DR. BARRY: I would call him about average for the series. These people with four years of invalidism and pain have a reason for being angry, antagonistic and suspicious.

DR. COBB: Was he especially sensitized by the behavior of his father?

DR. NEMIAH: I did not adequately bring out in the case presentation the need which this patient had to control doctors. He was not only critical of them but in the past had always tried to tell them how they should treat both himself and his family. He laid some emphasis on being a doctor's son and knowing how things should be done.

DR. BREWSTER: It is an unusual case. There are contrasts wherever you look. In the history you could make out a case for an infantile character, i.e., addiction, complaining attitude, demanding behavior, but you can see the opposite: a man with a well organized life, married, with children, successful in work with plenty of money to live on. There are these contrasts: in a man so successful it is unusual to find symptoms of such an infantile nature. It is surprising such infantile behavior disappeared so quickly. Was this a flight into health or a manic response? It is possible that he was one of those persons we see whose problem is that of an adult (e.g. adjustment to marriage) but who struggles with the problem on an infantile level. What might have been his adult problem? I wonder if it might have to do with his father and mother dying. Grief is at times expressed in infantile terms: e.g., with psychopathic behavior.

DR. NEMIAH: He was a man with very strong psychologic defenses which consisted in part of marked physical activity, and a need to be better than anyone else. There was considerable evidence that the patient was afraid of being dependent, and defended himself by his behavior, against wishes to be dependent. Having pain and symptoms gave him a seemingly legitimate excuse for being taken care of, which he could now seek in a demanding, infantile manner.

DR. DAWES: This patient's activity is very much like many adolescents one sees, and certainly activity is one of his defenses. When he was injured his defense of activity was removed from him, and a new pattern of behavior evolved. I believe the therapeutic process has consisted partly in letting him recreate his work patterns in occupational therapy and also in letting him verbalize some of his feelings.

DR. BONNER: I would wonder about the element of grief and punishment in this situation—factors I have found important in a number of pain problems I have worked with. I was impressed that his activity seemed to change after his parents' death; he attempted to handle his bereavement by becoming more and more active, which finally led to his injury.

DR. WEDROW: There was also his problem with being passive, which his aggressiveness and hostility was an attempt to deny. If his problem with passivity is important I wonder if the back injury and subsequent medical care does not revive all the difficulties in his relationship with his father—particularly in view of his associations to the traumatic tonsilectomy which are connected with his fear of cordotomy.

DR. LINDEMANN: This is a very complicated problem. My first reaction was that this might be a manic recovery from a depression. After a period of slowness and some retardation the patient assumes a high rate of activity, looking forward to relief in the future in the promised land in Florida. One wonders, however, how long he can keep this up. Another point that was interesting: one often sees patients who at first glance appear to be very sick psychologically, but who seem to have been very well organized people before they became ill. It is as though at the time of injury they had lost the defense of arranging things as they willed, and then encountered old problems from the past. It may be that a topical discussion of their problems will help to re-establish a set of defenses which had worked well for a long time before the injury even though they were not perfect. Therapy, in other words, has aimed here at a limited goal.

DR. NEMIAH: I agree about the re-establishment of limited goals, but my impression is that this occurred more as a result of my behavior with the patient, rather than from working through his problems verbally. I wondered, too, about his recovery being related to a manic phase, yet there was little, except for his increased activity, to substantiate such an impression—even at the end he had a rather slow, halting manner of speech and certainly lacked the spontaneity and euphoria one would expect in a manic state.

DR. BARRY: Was his initial picture really that of an endogenous depression? The depression found in patients with back injury is usually more reactive in character.

DR. COBB: I think it was a reactive depression and reactive elation afterwards. All of us have the mechanism in us of manic-depressives.

DR. BREWSTER: There is also an element of paranoid thinking in his relation to doctors.

DR. DAWES: I wonder if one can really call it paranoid—his father did attack him and hold him down.

DR. COBB: It was an extraordinary reality. He had a rather severe neurosis before the injury. He was a neurotic character. I think it is very worth while to try to reconstruct what we know of his character. If we can understand that, it will show us what sort of man reacts badly to injury.

DR. LINDEMANN: Much of his description of his former self is colored by his being depressed when describing it. I do not think, however, I could picture him as a going concern except as an obsessive, rigid, critical person, dependent on being appreciated and liked by people, remaining in equilibrium only if he keeps going at a considerable rate of activity. One wonders what will happen next, if he ever has to slow down again.

DR. COBB: I am afraid he has the kind of neurosis that is the product of our present culture in the United States. It is so common that it is considered "normal" by many people.

DISCUSSION

A number of important points are clear in this patient's disease. It is in the first place readily apparent that his illness was not an "either-or" affair, i.e., either psychiatric or orthopedic, organic or functional, mental or physical, or any of the other dichotomies so frequently made. There was ample evidence both by x-ray and observation at operation that he had a lesion involving the lumbosacral spine and sacral nerve roots—a lesion sufficient to give him pain. Knowing this one is tempted to accept it as the entire explanation for the patient's symptoms and disability. Treatment, then, is simple—remove the physical cause of the pain by cordotomy or other physical measures and, with symptoms gone, the patient will return to a normal life.

Such an attitude, however, ignores completely the possibility that psychologic factors are complicating the illness and contributing their share in producing the final clinical picture of a disabled human being in chronic distress. In this patient there was evidence of equal weight with

the evidence for a lesion, that emotional problems were important in his illness. As his treatment progressed it became apparent that his invalidism resulted almost entirely from emotional factors, and that the pain initially produced by his lesion was exacerbated and exaggerated by these same factors.

It was not just because the patient had failed to recover with the usual methods of treatment that psychologic factors were incriminated. When the patient was first seen by the psychiatrist, there were positive diagnostic features indicating the importance of an emotional disturbance—not as merely co-existent with his orthopedic symptoms, but as playing a significant role in their severity and morbidity.

The significant psychiatric observations were these: In presenting the history (1) the patient spoke not only of his injury and symptoms, but also spent a considerable amount of time describing what doctors and others had said to him, done to him, or not done for him. (2) He expressed a great deal of anger towards the doctors and ancillary personnel who had cared for him and voiced many complaints and suspicions about his management. (3) In describing his pain he used "agonizing," "excruciating" and other such emotionally toned adjectives and laid stress on the amount of "suffering" he had experienced. (4) He had failed to get significant relief from the usual orthopedic measures or from demerol to which he was addicted in large amounts. (5) He was obviously tense, anxious and somewhat depressed. (6) He was very demanding of the nurses and other ward personnel for medication and multiple small services. (7) He was often angry and critical if his wants were not supplied immediately.

These findings were sufficient to warrant postponing further surgery and transferring the patient to the psychiatric ward. The additional observations made in psychiatric interviews made it possible to elaborate upon aspects of his personality structure and emotional conflicts, which then gave a rational basis for therapeutic management.

In the three months of psychiatric contact with the patient it was obviously not possible to elucidate all the intracacies of his personality structure. However, certain observations were possible from which reasonable inferences were made concerning the nature of some of his conflicts. One was immediately impressed when first seeing this patient with the intensity of the demands he made for help for his pain, and with the anger which he showed when he felt he was being neglected. This was in striking contrast to his life-long behavior before his injury, which had been a pattern of exaggerated activity and self-sufficiency, along with a strong sense of "responsibility." The patient in fantasy pictured the alternative to this pattern as a state of complete irresponsibility and dependence which would "ruin a man's life."

One inferred from his demanding, angry reaction to pain that the patient's needs to be cared for were strong. In his own mind his dependent, invalid state was a result only of injury and pain; that he might have wishes to be cared for by others was inconceivable to him. On the contrary his concept of himself was of being a strong, self-sufficient, independent person, and his behavior prior to injury had fitted the pattern already described of extreme, exaggerated activity. This the patient felt arose from his "sense of responsibility." In other words his activity and energy represented to the patient a psychologic defense against dangerous desires for dependency, which he could not tolerate in himself, except insofar as the seemingly external agency of injury and pain had forced him into that role.

When injury and operation made it necessary for him to be inactive for a time, one of his important psychologic defenses was thereby temporarily lost to him. Moreover, as an invalid he could legitimately indulge his dependent needs, which with this outlet were expressed with great intensity in his complaints of pain and his demands referable to it, including his addiction to demerol; it was apparent that his needs were increasing and prolonging his symptoms. A partial explanation for the intensity and nature of his reaction to pain lay, then, in his psychologic makeup.

Obviously, however, his illness was not a satisfactory solution to his psychologic conflicts. Not only was he a total loss to his family economically and socially, but he was also extremely uncomfortable with his pain. Even more, his pain led to further emotional disturbance—in particular, desperate anxiety, anger and depression when he failed to get the help he needed, extreme enough at times to make him want to sign out of the hospital in the middle of the night or jump out of the window. It must also be kept in mind, that the patient was not aware of his dependent needs or their

influence on his illness. The slightest hint of them in interviews was disturbing to him. On the contrary he thought of himself still as a strong, independent person, kept down only by intractable pain. Only remove the pain, he felt, and he could function quite as he had before his injury. This continued conscious concept of himself as a strong, independent person was an important factor in his eventual recovery.

As has been mentioned a plan of management was devised, based partly on the knowledge gained from psychiatric interviews of the patient's feelings, fantasies and defenses. In the first place urging cordotomy on the patient seemed totally unadvisable in the face of his extreme anxiety about it and his conviction that complications from it would result in his being a helpless invalid. This negative approach to his problem was complemented by the positive psychotherapeutic plan. The basic aim was to establish a relationship with the patient in which he might regain his previous patterns of activity, which had acted as an adequate defense against his passive-dependent trends. The patient was accordingly allowed to make his own decisions about activity and treatment, within the limits of medical indications; the therapist refrained from any show of coercing the patient; he attempted to gratify the patient's many demands to provide necessary support for the patient's dependency, and keep him from panic and "signing out" of the hospital. As additional support the psychiatrist accepted all of the patient's complaints and hostility without comment or change in his own supporting behavior; this allowed the patient to release feelings which had played a partial role in his acute attacks of anxiety and depression. Finally, occupational therapy provided a tangible and practical outlet for his interests and physical activity.

There were several observations indicating that a restitution of the patient's psychologic defenses was an important feature in his recovery: on the ward he gradually became less demanding and complained less and less of his pain, as he grew more active, aggressive and domineering in his behavior. Coincidental with his increased self-confidence and activity, he was less preoccupied with his symptoms and began to make plans for his future, which he vigorously completed after discharge, moving his family south and embarking on a business venture which gave good promise of success. It was interesting that the patient's pain had not disappeared, but that, as the patient said, "it didn't bother him the way it used to." With a change in his psychologic equilibrium the pain no longer had the same emotional significance and function, and he was able to ignore the discomfort of the pain that still remained as a result of his back and nerve root lesions.

This patient's psychologic problem is not peculiar to back pain alone. It is a picture frequently seen when any chronic illness is complicated by emotional factors. Among the morals to be derived from this case presentation are these: (1) The possibility of emotional complications must be considered and evaluated in any patient with chronic illness, no matter what its origin. (2) There are often specific positive diagnostic signs indicating the presence of emotional factors, which are apparent during the doctor's first contacts with his patient. (3) Where such factors exist, the psychiatrist is helpful in elucidating the nature of the problem and planning therapy. (4) Therapy itself need not necessarily be the function of a psychiatrist. The role of an understanding supporting figure is one that every doctor can and often must fulfill in treating patients with chronic illness.

Clinico-pathologic Conference

Recurrent Jaundice, Chills, Fever and Abdominal Pain

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. G. (No. 219044), was a white retired business man, seventy-five years of age, who entered the Barnes Hospital on February 4, 1953, complaining of abdominal pain, chills and fever. The family history was non-contributory. Insofar as the past history was concerned the patient stated that he had been in good general health most of his life. He had had a bilateral inguinal herniorrhaphy some years prior to the present illness and more recently had undergone prostatectomy at another hospital.

In 1931 the patient developed upper abdominal pain and was hospitalized elsewhere. A cholecystectomy and appendectomy were performed. At operation multiple gallstones were found. The patient recovered uneventfully but a few months later again began to have pain in the left upper quadrant and chest. One day later he became jaundiced and a diagnosis of infectious hepatitis was made. Once again recovery was uneventful and the patient was well until 1941, ten years later, when he developed abdominal pain associated with leukocytosis. A gastrointestinal x-ray series at that time was said to have been negative. For several years prior to his Barnes Hospital admission the patient had had repeated episodes of abdominal pain associated with chills, the nature of which was unexplained. In May, 1952, he was found in his home in a comatose state by a neighbor, and on arrival at another hospital was moribund. His systolic blood pressure was 70 mm. of Hg, and on physical examination dyspnea, cyanosis and pulmonary edema were noted. Laboratory studies included the following: white blood cell count, 30,700, with a marked left shift in the differential count; hemoglobin, 14.2 gm. per cent; urine: 1 plus proteinuria and a marked increase in urobilinogen; carbon dioxide combining power, 33.4 mEq./L; non-protein nitrogen, 57 mg. per cent; total serum protein, 6.0 gm. per cent; albumin, 3.4 gm. per cent; globulin, 2.6 gm. per cent; icterus index, 38 units; cephalin-cholesterol flocculation test, 4 plus. Electrocardiogram: changes consistent with a posterior myocardial infarction.

The patient's pulmonary edema responded to the usual measures and he exhibited steady improvement. He was transiently anuric but his course was otherwise uneventful. After he recovered it was learned that the onset of his illness had been marked by abdominal pain and severe chills. At the time of his discharge from the hospital the non-protein nitrogen was 26 mg. per cent, the white cell count 9,500 and a repeat electrocardiogram was interpreted as showing only right bundle branch block. During his hospital stay x-ray studies revealed fibroid tuberculosis of the right upper lobe and a gastrointestinal series showed only a diverticulum of the second portion of the duodenum.

The patient then remained relatively well until he was seen by his private physician the day before entry to the Barnes Hospital at which time he stated that he had had diarrhea for ten days. He acknowledged, however, having taken laxatives during this period. For two days before entry he had had abdominal pain, chills and fever. During this period he had eaten and drunk very little. Although he was febrile and appeared dehydrated, examination revealed only a few scattered rales over the left lower lung field. The patient was given an injection of penicillin and urged to increase his fluid intake. The following day, however, he became drowsy, tachypneic, cyanotic and icteric and he was sent to the Barnes Hospital. Because of his marked lethargy, further historical information could not be obtained.

Physical examination at the time of entry revealed the patient's temperature to be 37.5°c., pulse 92, respirations 28, blood pressure 80/60. He was an elderly white male who appeared both acutely and chronically ill. He was quite obtunded. Respirations were deep but the patient was not cyanotic. He lay flat in bed and appeared to be most comfortable with his right thigh flexed against his abdomen. The skin was warm, dry, inelastic and icteric. The sclerae were also icteric. The pupils reacted normally to light and accommodation. Examination of the fundi revealed grade 2 retinopathy. The tongue was dry and coated. There was no significant lymph node enlargement. The neck was supple and the cervical veins were not distended. Examination of the chest revealed definite emphysema.

Dullness to percussion, decreased breath sounds and occasional rales at both lung bases were noted. The heart was not enlarged. The sounds were distant, the rhythm was regular and there was a soft blowing systolic murmur over the tricuspid valve area. The abdomen was somewhat distended and was hyperresonant to percussion. There was a well healed large scar and a ventral hernia in the right upper quadrant, and scars in the suprapubic and inguinal regions. On deep palpation of the epigastrium spasm and tenderness were noted, particularly on the left side. An occasional peristaltic wave, extending from the left to the right, was visible in the right upper abdomen and a few bowel sounds were heard on auscultation. The liver edge was felt 2 cm. below the right costal margin; the spleen could not be palpated. There was no costovertebral angle tenderness. Rectal examination was negative. The peripheral pulses were full and equal and there was no edema. Neurologic examination was negative.

Laboratory data were as follows: Blood count; red cells, 4,500,000; hemoglobin 15 gm. per cent; white cells, 21,800; differential count: 15 per cent juvenile forms, 20 per cent band forms, 59 per cent neutrophils, 4 per cent lymphocytes, and 2 per cent monocytes. Urinalysis: albumin, negative; sugar, negative; acetone, negative; foam test for bile, positive. Blood chemistry: non-protein nitrogen, 90 mg. per cent; blood sugar (while intravenous infusion of glucose was in progress), 140 mg. per cent; sodium 146 mEq./L; potassium, 3.9 mEq./L chloride, 88 mEq./L; carbon dioxide combining power, 31.1 mEq./L; total protein, 5.4 gm. per cent; albumin, 3.7 gm. per cent; globulin, 1.7 gm. per cent; alkaline phosphatase, 7.4 Bodansky units; prothrombin time, 70 per cent of normal; sodium bilirubinate, 6.28 mg. per cent; bilirubinglobin, 1.94 mg. per cent; cephalin-cholesterol flocculation test, 1 plus; thymol turbidity, 4.6 units.

The patient was given 400,000 units of penicillin intramuscularly twice daily and 0.5 gm. streptomycin intramuscularly four times daily; he also received fluids intravenously immediately upon admission and his blood pressure gradually increased over the next few hours. He continued, however, to be unable to urinate. A scanty specimen was obtained by catheterization but thereafter the patient was incontinent and oliguric. Early in the second hospital day he passed a voluminous dark stool which appeared grossly bloody. His blood pressure remained relatively stable at 100/50. The pulse was strong and regular at a rate of 80.

In the afternoon of the second day the patient's blood pressure fell rather precipitously to 80/40 and his pulse became grossly irregular. An electrocardiogram revealed auricular fibrillation with a ventricular rate of 110 to 120. The patient became more obtunded, abdominal distention increased and bowel sounds could no longer be heard. The previously visualized peristaltic waves disappeared. Cyanosis of the nail beds was noted and persisted despite the administration of oxygen by nasal tube. The patient began coughing up large amounts of brownish sputum and his temperature rose to 38°c. Gastric aspiration produced a liter of thin dark brown liquid which was guaiac positive. Wangensteen drainage was established and parenteral fluid therapy continued.

By the third hospital day the patient's blood pressure had risen to 110/60; his lungs remained clear on auscultation. The red blood cell count was 4,570,000 with 14.1 gm. per cent hemoglobin. The white blood cell count was 19,400, the differential showing 1 per cent myelocytes, 8 per cent juvenile forms, 30 per cent band forms, 54 per cent neutrophils, 4 per cent lymphocytes and 3 per cent monocytes. Shortly after noon on the third hospital day, February 6, 1953, the patient became increasingly cyanotic, his pulse was noted to be slow and weak; and although his blood pressure was well maintained, he expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This extremely interesting case is somewhat unusual in that the

present illness presumably covered a period of twenty-two years. The patient had his gallbladder removed in 1931, at which time definite stones were present. Several months thereafter he developed abdominal pain with jaundice and subsequently over the years had recurring attacks of abdominal pain, chills and fever; jaundice was also noted on at least several occasions. Twice gastrointestinal x-ray series were negative except for the demonstration of a duodenal diverticulum. He entered the Barnes Hospital because of an acute episode of relatively short duration, characterized by the gastrointestinal symptoms described in the protocol. At the time of entry he was distended and presented evidence of paralytic ileus. Dr. Taussig, would you open the discussion by telling us why you think this patient had recurrent episodes of chills, fever, abdominal pain and jaundice.

DR. BARRETT L. TAUSSIG: I would strongly suspect that the patient probably had a common duct stone with intermittent obstruction.

DR. ALEXANDER: As I have emphasized the patient did have gallstones at the time his gallbladder was removed twenty-two years earlier. If he had a common duct stone, it must have been present for twenty-two years or else it would have had to form *in situ*. Does that happen frequently?

DR. TAUSSIG: I think it happens although I am sure it is not common.

DR. ALEXANDER: In any case common duct stones certainly will have to be considered. Dr. Mendeloff, would you care to add anything?

DR. ALBERT I. MENDELOFF: I think there is no question that this patient had biliary tract disease over this long period of time, but if the history is correct I am impressed with the repeated rather serious episodes which occurred. On at least one occasion the patient apparently had a cardiovascular accident and was admitted to a hospital in a moribund state. The fact that he recovered from these episodes and did relatively well in the interim suggests to me that he also had acute recurrent pancreatitis.

DR. ALEXANDER: I assume you would relate the pancreatitis to the biliary tract disease?

DR. MENDELOFF: Yes, chronic or recurrent pancreatitis is usually associated either with biliary tract disease or with alcoholism. There is no evidence that this patient was an alcoholic or that his attacks followed alcoholic bouts. By exclusion, therefore, I would attribute them to biliary tract disease.

DR. ALEXANDER: Do you believe that the patient will have significant liver damage, Dr. Mendeloff?

DR. MENDELOFF: No, I do not. The fact that he recovered from his episodes of jaundice so rapidly and the fact that at the time of his last hospitalization there was no evidence of profound damage to the liver suggest to me that the organ was functioning relatively well.

DR. ALEXANDER: I do not mean to quibble, Dr. Mendeloff, but do you mean that the liver will be entirely normal or do you think it will show only minimal disease.

DR. MENDELOFF: I think it will show no evidence of biliary cirrhosis.

DR. ALEXANDER: Does everyone agree with that point of view?

DR. W. BARRY WOOD, JR.: I am not sure I would, Dr. Alexander. It seems to me that if a patient had as many attacks of acute obstruction as this man did over the years, with fever presumably due to cholangitis, his liver would show signs of biliary cirrhosis, at least to some degree.

DR. ALEXANDER: You predict then that the patient will have significant evidence of biliary cirrhosis?

DR. WOOD: Yes, I do. It is conceivable that the liver function tests could be reasonably normal and the spleen not palpable, despite the presence of biliary cirrhosis.

DR. ALEXANDER: Are there other suggestions?

DR. TAUSSIG: I would like to reiterate Dr. Mendeloff's suggestion of recurrent pancreatitis.

DR. MENDELOFF: In that regard mention should be made of a case we saw a year or so ago in which a duodenal diverticulum was demonstrated to be the cause of pancreatic obstruction and acute pancreatitis; this finding was most unusual but because the patient under discussion did have a duodenal diverticulum, I mention it. In the previous case the diverticulum blocked the accessory duct and the main pancreatic duct was absent.

DR. ALEXANDER: Would you enlarge on the relationship between the diverticulum and the pancreatitis.

DR. MENDELOFF: The diverticulum in the duodenum was on the medial side. It became ulcerated and edematous and produced complete blockage of the accessory pancreatic duct.

DR. ALEXANDER: Let us consider the events leading up to the patient's last admission. He had apparently had diarrhea for ten days, but during the period he had taken laxatives. For two days he suffered abdominal pain, chills and fever. At the time of admission he appeared acutely and chronically ill, but was most comfortable with his right knee flexed on his abdomen. On the initial examination bowel sounds were heard and peristaltic waves were seen but there was moderate abdominal distention. On the following morning the distention had increased and bowel sounds were no longer audible. A Levine tube was passed and a liter of fluid was found to be present in the stomach. Presumably then the patient had paralytic ileus. Dr. Mendeloff, would you discuss this entity. What is its mechanism and how does it arise?

DR. MENDELOFF: Paralytic ileus is a rather dramatic term which we use to describe cessation of propulsive activity in the gastrointestinal tract, usually in the small bowel and large bowel but often in the stomach as well. In general, paralytic ileus is described as due to either intra-abdominal or extra-abdominal factors. The intra-abdominal cause which is most common is peritonitis, either infectious or chemical. Other intra-abdominal causes of paralytic ileus are vascular accidents such as mesenteric thrombosis. This patient developed auricular fibrillation, and this fact brings to mind the possibility of embolus. Another cause of paralytic ileus which is considered intra-abdominal, although it is extraperitoneal, is the presence of lesions about the kidney which cause reflex peritoneal irritation, particularly perirenal hemorrhage or abscess.

Most of the extraperitoneal causes are associated with severe toxemia. Thus in many severe systemic diseases the intestinal tract becomes paralyzed just as it may under general anesthesia. The exact mechanism by which paralytic ileus is produced is not clear. It has recently been shown that early severe changes in blood electrolyte concentration may cause it, particularly the low potassium syndrome, but sodium depletion may likewise be responsible. It has been suggested that the final pathway by which paralytic ileus arises represents an abnormality at the neuromuscular junction in the intestinal wall.

DR. ALEXANDER: Dr. Massie, do you believe that the patient may have had an abdominal vascular accident?

DR. EDWARD MASSIE: No, I do not think so.

DR. ALEXANDER: On the second hospital day the patient's course took a dramatic turn for the worse. He passed bloody stools and gastric aspiration revealed guaiac positive secretions. On the other hand his blood count did not fall, his pulse rate did not rise and his blood pressure remained stable. Would you comment on the etiology of this episode, Dr. Schroeder?

DR. HENRY A. SCHROEDER: There is no question in my mind that the patient had bleeding into the gastrointestinal tract, but whether it occurred in a localized area or was widespread is difficult to say. I think he probably had a vascular accident which may have been venous rather than arterial.

DR. ALEXANDER: Would you consider seriously portal vein thrombosis?

DR. SCHROEDER: I believe it would be unusual. The possibility of peritonitis, which in a patient in this age group may not produce many signs, should be mentioned.

DR. ALEXANDER: The patient exhibited a marked hematologic response as evidenced by a leukocytosis between 19,000 and 36,000.

DR. MASSIE: Isn't it conceivable that there was ulceration and perforation of a common duct stone into the intestine, as a result of which bleeding occurred. One could also account for the pain, the leukocytosis and the localized peritonitis in this way.

DR. ALEXANDER: Your suggestion is an excellent one. Isn't it true that a marked inflammatory reaction results when a gallstone perforates the intestinal wall?

DR. MENDELOFF: Yes, it is.

DR. SCHROEDER: Did the physical findings suggest that the patient had psoas spasm? I ask that question because the patient kept his right thigh flexed on his abdomen?

DR. ALEXANDER: Dr. Dorsett, you examined the patient. Did you think he had any other signs of psoas spasm?

DR. DEWEY DORSETT: No, I did not.

DR. WOOD: Dr. Alexander, how definite were the peristaltic waves which were observed?

DR. ALEXANDER: Would you answer Dr. Wood's question, Dr. Dorsett?

DR. DORSETT: The patient had a large hernia at the site of the cholecystectomy scar. The peristaltic waves were seen through the wall of the hernial sac.

DR. WILLIAM H. DAUGHADAY: Dr. Mendeloff, isn't it true that gallstone ileus usually is due to

perforation of a stone from the gallbladder into the duodenum rather than from the common duct?

DR. MENDELOFF: Your statement is correct. There are probably four to five cholecystoduodenal fistulas for every choledochoduodenal fistula. On the other hand, in a case like the present one, it is difficult to know what happened. Although he had had a cholecystectomy, a remnant of the gallbladder may have persisted, become dilated and ultimately may have been the site of further stone formation. Such a stone may have perforated into the duodenum.

DR. ALEXANDER: In support of Dr. Daughaday's and Dr. Mendeloff's statements concerning the relative frequency of the two types of fistulas, in a series I found in the literature there were twelve cases of rupture of a common duct stone into the intestine in comparison to nearly 200 in which perforation of a stone from the gallbladder into the duodenum had occurred.

DR. WOOD: I would like to ask Dr. Mendeloff again about significance of the peristaltic waves. Is the recognition of peristaltic waves helpful in differentiating obstruction above and below the pylorus.

DR. MENDELOFF: It is difficult to be sure, particularly if one has to make his observations through the wall of a hernial sac. As a matter of fact, in many patients with hernias one can normally see peristaltic activity through the hernial sac.

DR. WOOD: In other words, you would discount that sign.

DR. MENDELOFF: I think it would be difficult to interpret.

DR. ALEXANDER: There is another question I would like to direct to Dr. Mendeloff. It concerns the marked leukocytosis which this patient exhibited with a number of his episodes. Isn't that feature more in favor of pancreatitis than of common duct obstruction?

DR. MENDELOFF: Your point is a good one. Pancreatitis may indeed produce a marked leukocytosis without much fever.

DR. ALEXANDER: I find it extremely difficult to assemble all the facts in this case into a straightforward clinical interpretation.

DR. MENDELOFF: It would be helpful if Dr. Massie would discuss the electrocardiographic findings.

DR. ALEXANDER: That information would be of interest, but before Dr. Massie gives it to us, I would like Dr. Smith to discuss the relationship between biliary and pancreatic lesions and cardiac symptoms.

DR. JOHN R. SMITH: The symptoms arising as a result of disease in the biliary and/or pancreatic tracts may be difficult to differentiate from those due to coronary artery disease. They notoriously produce pain referable to the epigastrium and to the retrosternal area; thus a clinical picture very suggestive of angina pectoris or myocardial infarction is frequently observed. More than one physician has been confused under such circumstances. Likewise pain arising in association with herniation of the stomach into the chest, with lower esophageal lesions, and occasionally with those in the duodenum, may simulate coronary pain. An additional point of importance, which adds to the problem of differentiation, is that in association with lesions in these various areas a barrage of noxious reflexes may be set up and these may manifest themselves by shock. In the present case, it is interesting to speculate on the origin of the auricular fibrillation which occurred when the patient's blood pressure fell. Auricular fibrillation is known to be associated with lesions of the auricular wall, atherosclerosis of the coronary system and with auricular distention coupled with vagus stimulation. A shock-like syndrome with sweating, nausea and vomiting can also probably be a precipitating cause of arrythmias and particularly of auricular fibrillation. The latter explanation may have been operative here. In association with attacks due to one of these intra-abdominal lesions, electrocardiographic patterns suggestive of coronary disease or coronary insufficiency may occur. These changes have been postulated to arise as a result of reflex coronary spasm but this hypothesis has been difficult to substantiate experimentally.

DR. ALEXANDER: Is it helpful to give such patients atropine to block the vagus?

DR. SMITH: It has not been in my experience.

DR. ALEXANDER: Dr. Massie, you have seen the electrocardiographic records. What is your opinion concerning the state of this man's heart? Was it compromised considerably or not?

DR. MASSIE: I don't think it was. The fact that he developed auricular fibrillation terminally is not unusual.

DR. ALEXANDER: It is of interest that this patient had a relatively elevated non-protein nitrogen and transient anuria in the past. Subsequently his non-protein nitrogen was normal. When he was admitted here there was

definite evidence of azotemia and he also had oliguria. Dr. Daughaday, would you comment on these observations?

DR. DAUGHADAY: This patient presented an example of what is usually called prerenal azotemia, a term which is rather misleading. It implies that the basic cause of the elevation of non-protein nitrogen is not renal failure but rather some extrarenal factor. Actually, in most instances there is probably some renal insufficiency in addition to the other factors which are operative. Probably circulatory failure of the kidney is an important factor, leading as it does to decreased glomerular infiltration with consequent retention of non-protein nitrogen. In some instances, particularly when there is increased formation of non-protein nitrogen due to toxic states, fever, etc., the non-protein nitrogen may rise rapidly. If the circulatory dynamics become further disturbed, ischemic necrosis involving the tubules may develop—so-called lower nephron nephrosis. Such a change is also reversible in many instances. As a matter of fact reversible renal insufficiency is really quite common in this age group.

DR. ALEXANDER: How do you explain the oliguria which occurred here?

DR. DAUGHADAY: It can really be explained by either mechanism. If glomerular filtration fails and reabsorption continues, the urine volume falls. On the other hand, if there is necrosis and rupture of the renal tubules the urine which comes into them diffuses through the interstitial tissues, causing marked edema and disruption of the continuity of many other tubules, a change which obviously leads to oliguria.

DR. ALEXANDER: I assume from your remarks that you would not be surprised to find definite vascular changes in this patient's kidneys.

DR. DAUGHADAY: That's correct. I doubt, however, that the changes of lower nephron nephrosis will be present.

DR. ALEXANDER: Dr. Sale, you followed this patient. Would you care to make any additional comments.

DR. LLEWELLYN SALE, JR.: As is indicated in the protocol this patient had an episode of jaundice in 1931, approximately five months following cholecystectomy. The information regarding subsequent bouts of jaundice is much less definite. He moved away from St. Louis and only returned in the year prior to his death. The episodes which he apparently suffered consisted primarily of abdominal pain which he always attributed to dietary indiscretion. Commonly constipation occurred for which he took laxatives. He then would develop diarrhea, fever and chills, but usually would recover in twenty-four to forty-eight hours. The episode in May, 1952, certainly seemed to me to have represented a vascular accident.

It should be noted that the patient had senile emphysema and the only time I saw him he had a number of coarse rales and rhonchi throughout the lung fields. A question arose whether the acute episode in May, 1952, could have been due to a pulmonary infarction followed by transient mild jaundice arising as a result of the infarction. Actually his course between the episode in May, 1952, and his terminal illness was very benign in that he was essentially free from complaints. Evaluation of the history is made all the more difficult because the patient was somewhat unreliable.

DR. ALEXANDER: When he was in the hospital in May, 1952, the icterus index was 38. When was that determination made?

DR. SALE, JR.: About two to three days after admission.

DR. ALEXANDER: How long before do you think the pulmonary infarction, if he had one, probably occurred?

DR. SALE, JR.: That is hard to say. The patient had been ill at home for several days before being admitted to the hospital.

DR. ALEXANDER: Approximately how long does it take for jaundice to develop after a pulmonary infarction.

DR. MENDELOFF: I believe it takes a week.

DR. ALEXANDER: It should be remembered that on the admission in May, 1952, the patient had a 4 plus cephalin-cholesterol flocculation test; presumably he may have had significant liver impairment at that time.

DR. WOOD: Dr. Alexander, it was difficult to get an adequate history from this man, as Dr. Sale has indicated, and we are therefore in a difficult position in trying to arrive at a final diagnosis. I would like to ask Dr. Mendeloff whether this patient could have had cholangiolitic cirrhosis. Do you believe it is possible that the patient had epidemic hepatitis in 1941 followed by this complication?

DR. MENDELOFF: Most of those patients have marked hepatomegaly, Dr. Wood; I would also find it difficult to explain the marked leukocytosis on that basis.

DR. ALEXANDER: Although as you have pointed out, Dr. Wood, it is difficult to be very certain about the clinical diagnosis in view of the lack of an adequate history, would you care to state your conclusions?

DR. WOOD: I think the patient most likely had a stone in the common duct, probably with acute pancreatitis and some biliary cirrhosis; as an alternate but much less likely explanation, I would suggest a fistulous tract between the common bile duct and the intestinal tract.

DR. ALEXANDER: In summary, the majority opinion favors a stone in the common duct with recurrent pancreatitis and biliary cirrhosis as associated findings. A less likely possibility is that a fistulous tract between the biliary system and the intestine exists. It is predicted that the patient will not have significant coronary artery disease.

Clinical Diagnoses: Common duct stone; acute recurrent pancreatitis; ? biliary cirrhosis; ? fistulous tract between the biliary system and intestine.

PATHOLOGIC DISCUSSION

DR. JOHN KISSANE: The external examination showed a moderate degree of generalized icterus. There were 50 ml. in the left pleural cavity and 10 ml. in the right of clear, straw-colored fluid with the specific gravity of a transudate. The lungs weighed 1,400 gm. and were moist and of diminished crepitance. Both apices contained areas of fibrosis and chalky areas of caseation. The heart was enlarged, weighing 530 gm. The myocardium of the septum showed small flecks of fibrosis. The circumflex branch of the left coronary artery was narrowed by an advanced degree of arteriosclerosis. The other coronary arteries were only slightly sclerotic. There were dense fibrous adhesions about the fossa of the gallbladder. A band of adhesions to the anterior abdominal wall distorted a portion of the first part of the duodenum to produce a pseudodiverticulum. The common bile duct was greatly dilated, measuring 5 cm. in circumference. Its wall was thick and fibrous. The stump of the cystic duct was recognizable as a blind pouch 1 cm. in length. On opening the common bile duct a 1 by 2 cm. rough, barrel-shaped calculus was exposed 2 cm. above the ampulla. Between this point and the duodenum the bile duct narrowed to a normal diameter at the ampulla. This narrowed portion contained eight 0.5 cm. facetted stones. Beneath the large obstructing calculus there were shallow chronic ulcers in the mucosa of the common bile duct. There were innumerable 0.5 to 1 cm. soft brown stones in the common, hepatic and intrahepatic bile ducts above the large calculus. The kidneys showed slight arteriolar nephrosclerosis but were of normal size. There was no point of mechanical obstruction in the intestine. A few erosions were present in the mucosa of the stomach, and in the distal ileum, cecum, transverse colon and rectum there were patches of confluent superficial necrosis covered by a delicate, filmy, grey yellow membrane.

DR. DAVID E. SMITH: The pathologic lesions in this case can be divided into three principal categories: first, those in the biliary tract, second those in the heart, and third those in the gastrointestinal tract. The gallstones in this patient's greatly dilated bile ducts pose an interesting problem. Were they formed in the gallbladder and displaced into the bile ducts before the cholecystectomy twenty-two years previously, or were they formed in the dilated bile duct after the operation? The fact that the bile duct was so tremendously dilated suggests that this was not an uncomplicated case of cholelithiasis and cholecystectomy. Rather, there was probably a common duct stone that was intermittently obstructing the duct at the time there was still a gallbladder to relieve partially the increased pressure and allow hypertrophy and dilatation of the duct. Complete obstruction or simple cholecystectomy do not usually lead to the extreme degree of hypertrophy and dilatation seen in this case.

The large barrel-shaped stone which was found 2 cm. or so above the ampulla, and which overlaid the ulcers in the common duct, was composed of two components. On its cross section there was a dark green ring about a third of the distance beneath the surface. Within this ring the structure was of the type usual for facetted inflammatory gallstones with broken radial arrangements of cholesterol crystals and pigment and central liquefaction. This is typical of a stone formed in the gallbladder. On the other hand, the outer portion of this stone was quite irregular and of crumbly, homogeneous, yellow-brown substance which, particularly when damp, crumbled very easily under pressure. The stones distal to this were perfectly typical gallbladder stones. They were smaller than the large stone and had a facetted shape and a smooth uniform surface except where points

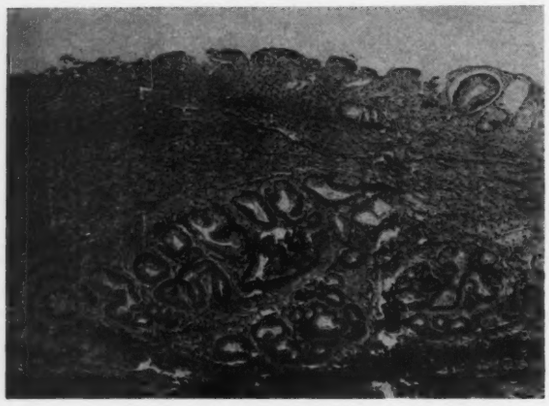

FIG. 1. A section of the greatly dilated and hypertrophied common bile duct showing chronic inflammation and fibrosis of the lamina propria.

of grinding contact with one another had exposed the central laminations. The stones proximal to the large obstructing stone, however, were of a different type. They could be crumbled between one's fingers into a soft granular material. The largest of these stones were above the large obstructive combination stone, but smaller examples were found in the intrahepatic bile ducts. These so-called stasis stones are characteristic of stones formed in the biliary tract and not in the gallbladder. I think from the nature of the stones themselves we can say that they were gallstones that were formed in the gallbladder and displaced into the common duct before this patient had his gallbladder removed. One of these stones was perhaps larger than the others and formed a nucleus the volume of which was increased by the precipitation of bile from the bile duct onto its surface, until it was eventually sufficiently large to be obstructive. Perhaps the first episode five months after the cholecystectomy was due to the stone that had been left in the common duct. The later episodes of jaundice were probably related to the increase in size and intermittent obstruction caused by the enlarging combination stone. The duct stones proximal to the large one were the result of later stasis in the extrahepatic and intrahepatic bile ducts.

The microscopic preparations relative to this phase of the patient's illness are from the bile duct and the liver. Figure 1 is from the surface of the large ulcerated bile duct. The mucosa is denuded although this is not actually one of the ulcers. In the lamina propria and about the mucous glands is an inflammatory infiltration of considerable intensity. The thickened and densely fibrous wall of this structure is also shown. The ulceration and chronic inflammation in this large dilated duct are evidence of what was probably a relapsing infection responsible for the clinical episodes of fever. The liver in Figure 2 shows the rather slight amount of change in that organ. There was no grossly recognizable cirrhosis and microscopically there are only a few extra bile ducts and slightly enlarged portal spaces with a slight infiltration of inflammatory cells. This is a slight degree of biliary cirrhosis and pericholangitis, but not much more.

The second part of this patient's illness was contributed by his cardiovascular system. The heart was definitely enlarged. Although the clinical history does not record any hypertension, we can reasonably presume this patient must have had an overworked heart. In the capsule of the adrenal, as illustrated in Figure 3, there were blood vessels with a remarkable degree of arteriolar and small artery arteriosclerosis typical of hypertension. This figure is simply a convenient illustration of a generalized process that was also manifest in the kidney as a distinct amount of arteriolar nephrosclerosis. Grossly the heart showed particularly prominent arteriosclerosis of the circumflex coronary artery and small foci of fibrosis in the myocardium of the septum and posterior wall of the left ventricle. In the microscopic sections there were smaller and more widely disseminated foci indicative of the loss of a few muscle bundles and an increase of interstitial fibrous tissue such as that shown in Figure 4. This is characteristic of a compromised coronary circulation and repeated small damage limited to the myocardium. This type of lesion is also the only anatomic clue that seems related to the rather dramatic episode of coma which may have been the result of cardiac arrhythmia and cerebral anoxia.

The last section (Fig. 5) is of one of the erosions overlaid with a pseudomembrane that were present in the ileum and colon. It shows the very superficial nature of the necrosis, the diphtheritic membrane of fibrin and débris over edema and slight inflammation in the lamina propria and submucosa. This lesion may well be related to the terminal episode of abdominal pain, diarrhea, fever and possible melena. It is not a specific enterocolitis but is typical of lesions often found in patients with other primary diseases and generally interpreted as a terminal event.

By way of recapitulation, this patient had

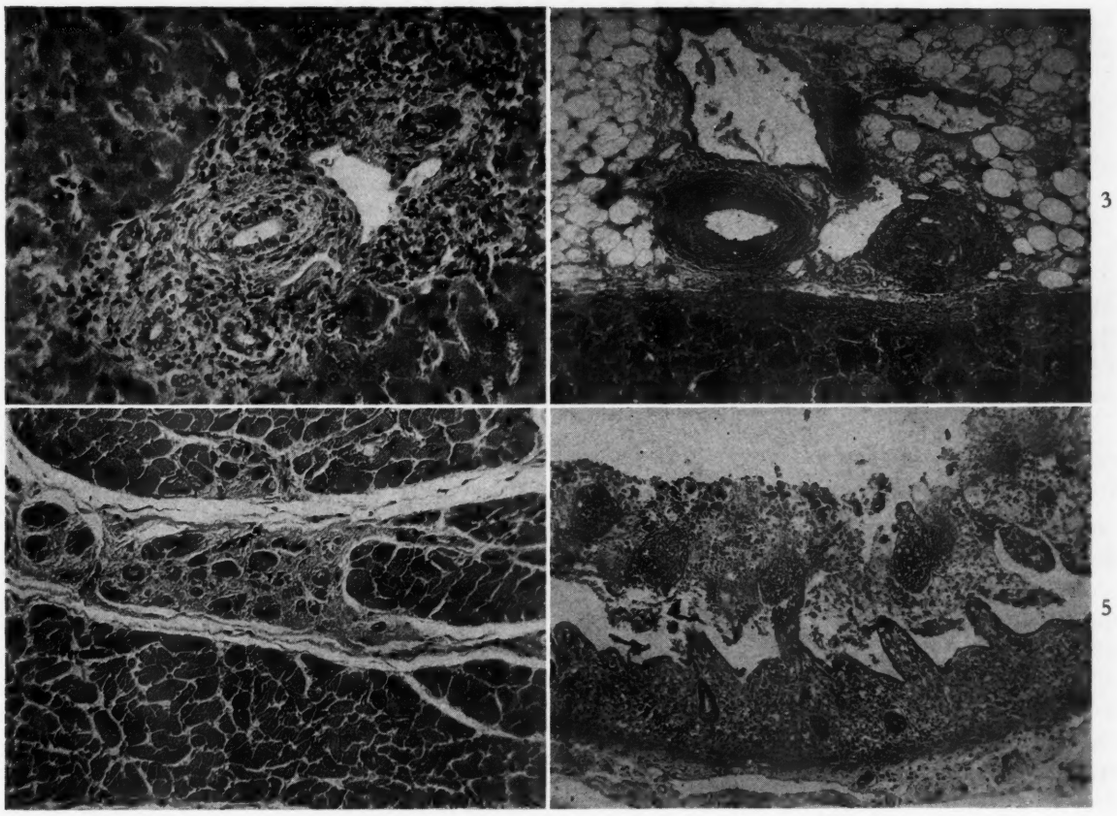

FIG. 2. A portal space in the liver with slight increase in fibrous tissue, slight proliferation of bile ducts and increased lymphocytes and leukocytes indicative of the very slight damage caused by prolonged disease of the biliary tract with intermittent obstruction.

FIG. 3. Thickened arterioles and small arteries in the capsule of the adrenal representative of the general vascular status.

FIG. 4. An example of the disseminated foci of microscopic fibrosis in the myocardium which resulted from chronic coronary artery insufficiency.

FIG. 5. An ulcer overlaid with pseudomembrane from one of the disseminated lesions of necrotizing enterocolitis.

cholecystitis and developed gallstones more than twenty-two years before his death. Some of these stones passed into the common duct, causing partial obstruction and hypertrophy and dilatation of the duct. He was operated upon and the gallbladder removed but some stones were left in the bile duct. One of these stones increased in size and led to intermittent episodes of jaundice and later to ulceration and chronic inflammation of the bile ducts from which were derived not only the episodes of jaundice but also of fever. These events were apparently neither very prolonged nor very intense as the liver was not severely compromised. During the same period of time he developed arteriosclerosis on an extensive basis, including particularly the coronary arteries, and myocardial damage gave rise to arrhythmias, syncope and periods of failure. Finally, he developed, as a terminal manifestation, necrotizing colitis and ileitis.

Final Anatomic Diagnoses: Choleliths and choledocholiths in the bile ducts; subacute and chronic cholangitis; obstructive biliary cirrhosis, minimal; arterial and arteriolosclerosis; focal fibrosis in the myocardium; focal necrotizing enterocolitis.

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Research Society Abstracts

Western Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SIXTH ANNUAL MEETING, CARMEL, CALIFORNIA, JANUARY 30 AND 31, 1953

ENDOCARDIAL FIBROELASTOSIS: REPORT OF UNUSUAL CASE WITH IMPAIRED ABILITY TO FABRICATE SERUM PROTEINS. *Forrest H. Adams and Ben E. Katz, (Introduced by John M. Adams)*, Dept. of Pediatrics, U.C.L.A. School of Medicine, Los Angeles, Calif., and the Univ. of Minnesota, Minneapolis, Minn.

Hypertrophy of the heart, primarily of the left ventricle, associated with or due to endocardial fibroelastosis occurs usually in small infants. Generally speaking most of the patients die within twenty-four to forty-eight hours after the apparent onset of symptoms so that there is little opportunity to make extensive clinical observations. The authors have studied twenty-two patients with endocardial fibroelastosis in some of whom observations were made over a period of months and years. In eighteen of the patients the diagnosis was confirmed at autopsy.

Three clinical patterns have been noted: (1) Sudden death frequently following respiratory disease, eleven cases; (2) progressive dyspnea and heart failure, four cases; (3) repeated episodes of heart failure, seven cases. Physical examination usually revealed an acutely or chronically ill infant with fever, dyspnea, cyanosis, rales in the lungs, cardiomegaly, sometimes hepatomegaly but usually no peripheral edema. A mitral or aortic murmur was heard in some but not in others. Laboratory tests, including those involving the "acute proteins," were normal. Electrocardiogram revealed a normal or left axis deviation with evidence of left ventricular hypertrophy. In addition, low, negative or diphasic T waves and depression of the S-T segments were noted in some. Roentgen examination usually revealed a markedly enlarged left ventricle.

Extensive clinical studies made on a six year old child with endocardial fibroelastosis will be reported. This patient had peripheral edema and ascites as his major manifestation of the disease. Studies revealed low plasma proteins secondary to inability of the liver to fabricate serum proteins.

* Asterisks indicate member of the Society.

PREVENTION OF PARALYTIC POLIOMYELITIS IN TONSILLECTOMIZED CYNOMOLGUS MONKEYS BY HUMAN GAMMA GLOBULIN. *J. M. Adams,* R. A. Boak, C. M. Carpenter, J. D. French, S. J. Klein, J. J. Pressman and J. L. Smith*, Dept. of Pediatrics, U.C.L.A. School of Medicine, Los Angeles, Calif.

In four different experiments 156 animals fed poliomyelitis virus have been studied; of this total 117 were tonsillectomized, and thirty-nine animals not operated upon made up the control groups. Our primary purpose was to demonstrate the protective effect against the disease of concentrated human gamma globulin in tonsillectomized monkeys and to determine the dose necessary for modification or prevention. Tonsillectomized cynomolgus monkeys were protected from paralytic poliomyelitis by human gamma globulin when a dose of 2 ml. per pound was administered *prior* to feeding virus. Nine of ten passively protected animals have resisted rechallenge with the poliomyelitis virus, suggesting that the monkeys acquired immunity.

The poliomyelitis attack rate in the tonsillectomized animals was 65 per cent; in the animals which were tonsillectomized and given gamma globulin it was 12 per cent; and in the non-operated control animals it was 13 per cent. In the last experiment nine of eleven tonsillectomized monkeys and ten of eleven tonsillectomized monkeys also given Coxsackie virus developed poliomyelitis. None of the eleven animals injected with human gamma globulin prior to operation developed paralytic disease.

An attempt to inhibit poliomyelitis in monkeys by means of simultaneous infections with distemper or Coxsackie viruses failed. The animals given Coxsackie viruses intraperitoneally developed profuse nasal discharge forty-eight hours after inoculation, and the

viruses were isolated from this material as well as from the stools.

HUMAN PLASMAPHERESIS. *William S. Adams,* William H. Blahd, William G. Figueroa and Samuel H. Bassett,** Dept. of Medicine, U.C.L.A. School of Medicine, Los Angeles, Calif.

A case of multiple myeloma was the subject of a prolonged study of nitrogen exchange before, during and after plasmapheresis. The removal of plasma during the experimental periods was carried out daily and the patient's own red blood cells were returned to his circulation. An average of 30 gm. of plasma protein were removed per day and a total of 30 L. of plasma were removed over a period of eighty-five days. Despite this tremendous loss of plasma protein very little fluctuation in the concentration of the normal or abnormal plasma proteins was detected. Plasma protein fractionation was carried out both by chemical and electrophoretic means. It is apparent from this study that this patient demonstrated an excellent capacity for regeneration of his plasma proteins, and that with an adequate intake of protein he was able to compensate almost completely for the losses incurred due to plasmapheresis. At a lower dietary level of protein intake compensation was not complete and over a prolonged interval serious protein deficits would be expected.

A similar study was carried out on a normal subject while on a dietary regimen containing 96 gm. of protein and 2,000 calories per day. Following an initial control period of fifteen days 14.1 L. of plasma were removed over the course of twenty-five days. The plasma protein concentration fell from control values averaging 6.8 gm. per cent to 5.7 gm. per cent. From electrophoretic and chemical fractionation studies it would appear that the major protein which was depleted was the gamma globulin. The effect of diet on the ability of an individual to regenerate plasma proteins is discussed in the light of these and other metabolic data.

PROTRACTED SHOCK IN THE CLOSED-CHEST DOG FOLLOWING CORONARY EMBOLIZATION WITH GRADED MICROSPHERES. *Clarence M. Agress,* Marvin J. Rosenburg, Howard I. Jacobs, Maxwell J. Binder, Abraham Schneiderman and William G. Clark,* Veterans Administration Centre, Los Angeles, Calif.

A method has been devised for controlled embolization of the coronary circulation in the closed-chest dog. By this means chronic or acute injuries may be produced and studied without introducing the factors of trauma and hemorrhage inherent in open-chest technics. Blood pressure falls interpreted as coronary shock have been produced for periods up to fifty hours. The criteria of shock have been defined as follows: (1) Reduction of approximately 30 per cent in mean arterial blood pressure; (2) maintenance of this reduction in blood pressure with no upward trend for at least thirty minutes; (3) electrocardiogram evidence of severe myocardial ischemia; (4) absence of arrhythmias, such as heart block, which could account for the blood pressure reduction; and (5) evidence at autopsy that the heart was severely damaged. It has been found that the blood pressure fall is a critical function of the size of the embolus. The effective emboli were plastic microspheres of approximately 325 μ diameter, or mixed microspheres ranging in diameter from 190 to 247 μ.

Evidence from quantitative studies by gravimetric and radioactive methods suggest that the caliber and not the number of vessels occluded is the determining factor in the production of this type of experimental shock.

EXPERIMENTAL PRODUCTION OF PORPHYRIA IN THE RAT. *Robert A. Aldrich,* James D. Case and Richard A. Nevé,* Dept. of Pediatrics, Univ. of Oregon Medical School, Portland, Ore.

Mature Sprague-Dawley rats receiving daily oral doses of allyl-isopropyl-acetyl-carbamide (sedormid) develop clinical and chemical changes which closely resemble porphyria in human adults. Within a few days the excretion of urinary coproporphyrin rises to a high level. Uroporphyrin, normally present in the urine in very slight traces, is excreted in huge quantities after a variable lag phase. There appears to be considerable difference in the susceptibility of these animals to the same dose of the drug. As a result the lag phase is unpredictable. Massive excretion of uroporphyrin develops abruptly soon after the appearance in the urine of a strongly positive porphobilinogen test. Most of this uroporphyrin is in the form of a colorless chromogen that can be converted to uroporphyrin by heat at pH 5.0. At least 85 per cent of the coproporphyrin has the type III isomeric configuration.

Clinically weakness of the hind quarters develop in the animals about the time massive

excretion of uroporphyrin occurs. If the drug is continued, death follows and gross dilatation of the gastrointestinal tract is a prominent feature at autopsy. On the other hand, if the drug is withdrawn, porphyrin metabolism quickly becomes normal and the animal recovers.

AUTO-REMOVAL OF LEUKOCYTES FROM THE PERIPHERAL CIRCULATION OF MAN INITIATED BY ADMINISTRATION OF ANTI-GROUP SPECIFIC SUBSTANCES. *Howard R. Bierman,* Keith H. Kelly, Ralph L. Byron, Jr., Fauno L. Cordes, Laurens P. White and Aline Littman*, The Laboratory of Experimental Oncology. Dept. of Medicine, Univ. of California School of Medicine, San Francisco, Calif.

Exploration of various methods to stimulate the normal leukocyte removal mechanisms has revealed that intravenous administration of anti-group specific substance will cause a profound and protracted decrease in peripheral leukocyte count. The anti-group specific substance was administered as freshly drawn whole blood over periods of one to sixty minutes. The infusion of 5 to 35 cc. of A+ blood into O+ recipients and B+ blood into A+ recipients on fourteen occasions in ten patients resulted in 30 to 90 per cent decrease in leukocyte number, often below 1,000 per cm., which persisted for periods of ten minutes to two hours. Both rate of administration and amount of infused blood were significant in determining the degree and duration of the leukopenia. Intravascular erythrophagocytosis was observed within thirty seconds after the initiation of the infusion, often after only 2 to 3 cc. of anti-group blood had been administered and usually before the leukopenia developed.

Four patients with various leukemias also proved capable of removing abnormal leukocytes from the peripheral circulation under the influence of the anti-group blood. Erythrophagocytosis by mature and immature granulocytes, monocytes and monoblasts was observed. Lymphocytes in the patients with lymphocytic leukemia were reduced significantly but they did not exhibit phagocytosis of red cells.

The site of removal of leukocytes under these circumstances was not limited to any single organ. Intravenous or intra-arterial administration did not alter the findings materially. Intrasplenic administration delayed the appearance of the nadir. Aside from transient flushing and moderate dyspnea in two patients with pulmonary insufficiency, there were no immediate or late untoward effects. No urinary abnormalities were detected.

Repeated administration of smaller amounts of anti-group substance at five- to seven-day intervals was followed by increasingly profound effects.

THE RIGHT ATRIAL PRESSURE WAVE ASSOCIATED WITH RIGHT VENTRICULAR HYPERTROPHY. *S. Gilbert Blount, Jr., Malcolm C. McCord and Seichi Komesu* (*Introduced by Gordon Meiklejohn*), Dept. of Medicine, Univ. of Colorado Medical School, Denver, Colo.

It has been observed in this laboratory that the right atrial pressure wave exhibits a consistently similar configuration in patients with lesions causing marked right ventricular hypertrophy. In order to define the mechanisms producing this characteristic wave an analysis has been made of the right atrial pressure waves in patients with isolated valvular pulmonic stenosis and with idiopathic pulmonary hypertension. These entities were selected because they most often result in the most severe degrees of right ventricular hypertrophy.

In thirteen of fifteen patients with pulmonic stenosis the right atrial pressures revealed an abnormally high wave occurring 0.06 to 0.09 seconds following the P wave of the electrocardiogram. The amplitude of this "a" wave ranged from 8 to 17 mm. Hg. The right ventricular systolic pressure ranged from 47 to 221 mm. Hg; the diastolic pressure was within normal limits in all cases. The catheter was passed through the foramen ovale in four patients with peripheral arterial unsaturation and a pressure gradient from the right to the left atrium was demonstrated. The right atrial pressure tracing revealed giant "a" waves in five of six patients with idiopathic pulmonary hypertension, these waves ranging from 13 to 27 mm. Hg in amplitude. In both groups there was a relationship between the amplitude of the "a" waves and the amplitude of the P waves, the intrinsicoid deflection time in lead V-1, the size of the right atrium, and the presence of presystolic pulsations in the neck veins.

The giant "a" wave is thus a manifestation of the altered pressure-volume relationship of the right ventricle during diastole. The loss of the normal distensibility of the hypertrophied

right ventricle results in an increased residual blood volume in the right atrium and consequent hypertrophy of this chamber.

MECHANISM OF ACTION OF SYMPATHETIC BLOCKS IN RELIEF OF PAIN. *Ellen Brown,** Dept. of Medicine, Univ. of California School of Medicine, San Francisco, Calif.

Patients suffering from pain syndromes of obscure etiology frequently derive temporary benefit from sympathetic block. This suggests that the sympathetic nervous system may be directly involved in perpetuating such disturbances, although this relationship has not been proved.

As part of a comprehensive study in which a wide variety of therapeutic and diagnostic tests were applied to patients with chronic deep limb or phantom pain, the effects of vasodilating drugs, procaine blocks and sympathectomy were observed. The completeness of sympathectomy was appraised by sweating tests, and vasomotor effects by measurements of surface temperature. Of sixteen patients who received intravenous injections of tetraethylammonium chloride (5.0 to 8.9 mg./K) the majority manifested vasodilatation but only one experienced relief of pain. This patient manifested general vasodilation but the involved extremity failed to become warm. Intravenous injections of priscoline (50 mg.) produced vasodilatation but no relief of pain in each of four subjects so treated. Stellate or lumbar blocks with procaine relieved pain transiently in five of eight cases. In one of these no benefit resulted from subsequent surgical sympathectomy. One patient who had undergone upper thoracic sympathectomy previously, with resultant vasoparalysis and anhidrosis but persisting pain in arm and hand, was relieved by stellate block. In three cases injection of procaine into the shoulder muscles resulted in relief comparable to that effected by stellate block, without causing signs of sympathetic paralysis.

These observations suggest that relief of pain by sympathetic blocks depends neither on the production of vasomotor paralysis nor on interruption of afferent pain pathways, and may indeed be non-specific.

VARIATIONS IN ELECTROLYTE RESPONSES TO MITRAL VALVE SURGERY. *R. A. Bruce,** *M. F. Dunning and K. A. Merendino*, Depts. of Medicine and Surgery, Univ. of Washington, Seattle, Wash.

It has been our observation that some of the patients with mitral stenosis who have been submitted to surgical treatment and have had complications in the early postoperative period with delayed recovery had been on a low-salt intake and occasionally received a mercurial diuretic preoperatively. They had been deprived of salt during the early postoperative period because of the hazard of pulmonary edema. One patient exhibited a transient depression of cerebral function and was observed to have serum Na and Cl values of 118 and 69 mEq./L., respectively.

Of the next ten patients submitted to operation seven had serum Na values under 130 mEq./L.; two were as low as 120 and 113 mEq./L. Eight patients had Cl values under 90 mEq./L. and two of these were less than 70 mEq./L. There were slight changes in serum K and the CO_2 varied from 19 to 31 mEq./L. Restoration of normal Cl values tended to take longer than Na. All excreted only small amounts of Na in the urine during the first week postoperatively. The two patients with the lowest serum Na values required intravenous saline to relieve disturbances in cerebral function. In contrast, another patient exhibited cardiac dilatation, venous hypertension and impaired exercise tolerance within the first two weeks. This patient continued to excrete only small amounts of Na in the urine for over a month and marked hyponatremia and hypochloremia never occurred.

Thus hyponatremia has been observed in some of the patients following mitral valve surgery; this response may be an exaggeration of the normal electrolyte response to surgical trauma. The effects and risks of prophylactic sodium or potassium therapy during the early postoperative phase are being investigated.

TRANSFER OF SUSCEPTIBILITY TO DIETARY HYPERCHOLESTEREMIA FROM THE RABBIT TO THE NORMAL RAT. *Sanford O. Byers,** *Meyer Friedman,** *Ray H. Rosenman*, The Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

The rat is resistant to alimentarily induced hypercholesteremia while the rabbit is characteristically susceptible. The mechanism responsible for this extreme variation in response to oral cholesterol is of great interest clinically as it may point the way to practical prophylaxis of atherosclerosis. The site of this mechanism has been found to reside in great part in the plasma

of the rabbit, for when the plasma of nine rats was removed and replaced by normal rabbit plasma, the rats showed a hypercholesteremic response (i.e., a rabbit type of hypercholesteremia) when given excess dietary cholesterol. Thus the average plasma cholesterol of these rats rose 130 per cent in forty-eight hours. No comparable rise, however, appeared in five rats given the same transfusion of rabbit plasma but kept on a cholesterol-free diet, nor did untreated control rats show hypercholesteremia when placed on a high cholesterol diet. The peculiarity of rabbit plasma is probably a high capacity of plasma protein to bind exogenously derived cholesterol.

INFLUENCE OF ANTIBODY ON ANTIBODY FORMATION. *Dan H. Campbell,** Div. of Chemistry and Chemical Engineering, California Inst. of Technology, Pasadena, Calif.

A large number of experiments have been carried out during the past three years in an effort to determine if circulating antibody has any effect upon the antibody-forming efficacy of specific antigen. Using rabbits as the experimental animal and a crystalline bovine serum albumin antigen system it was found that antibody would enhance the immunizing power of antigen. This effect was particularly evident when antigen and antibody was injected as an insoluble complex. Insolubility *per se* was not the basis of this effect since, under the experimental conditions used, alum-precipitated albumin gave essentially the same results as soluble albumin. The "priming" effect of antibody was evident by (1) a more rapid appearance of antibody; (2) a much greater amount of antibody in a short period of immunization; and (3) a marked reduction in the number of negative animals was also noted. These results suggest the practicality of enhancing immunization procedures against infectious agents or toxins.

ERYTHROPOIESIS IN PERNICIOUS ANEMIA. *Daniel H. Coleman and Clement A. Finch,** Dept. of Medicine, Univ. of Washington Medical School, Seattle, Wash.

B_{12} deficiency produces bone marrow hyperplasia with maturation arrest and a macrocytic anemia. Although red cell survival time is shortened, there is evidence that most of the hemoglobin pigment catabolized is not derived from circulating erythrocytes. In the present studies both qualitative and quantitative aspects of erythropoiesis in pernicious anemia have been determined.

Measurements include serum iron turnover, red cell utilization of radioiron, bone marrow differential counts, serum bilirubin, reticulocyte counts and stool urobilinogen. Data obtained from patients with pernicious anemia in relapse and in response to therapy will be presented. The conclusions reached may be summarized as follows:

While red cell delivery from the marrow to the peripheral blood is subnormal, hemoglobin synthesis and degradation within the marrow occur at a rapid rate. This intra-marrow hemolysis ceases with B_{12} therapy; synthesized cells are then delivered in larger numbers to the peripheral blood. Once the source of iron derived from intra-medullary erythrocyte destruction is cut off, hematopoiesis is limited by the rate at which tissue iron can be mobilized. Subsequent rates of erythropoiesis during recovery are comparable to regeneration of blood in phlebotomized patients with adequate iron stores.

RESPONSE OF CIRCULATING 17-HYDROXYCORTICOSTEROIDS TO SALICYLATE. *Alan K. Done, Robert S. Ely and Vincent C. Kelley,** Dept. of Pediatrics, Univ. of Utah College of Medicine, Salt Lake City, Utah.

Recent indirect evidence has suggested that high doses of salicylate produce stimulation of the adrenal cortex. To investigate this relationship further we have studied in man and animals the effects of salicylate administration in various doses by measuring levels of 17-hydroxycorticosteroids, eosinophils and salicylates.

Guinea pigs given large single doses of salicylate showed marked elevation of 17-hydroxycorticosteroids. Patients with salicylate intoxication also showed marked elevation of these steroid levels. However, of control human subjects given massive doses of salicylate only 50 per cent showed significant elevations during the study period. Whereas about two-thirds of this group showed significant eosinopenia, no consistent correlation between eosinophil change and steroid levels was apparent. A more consistent finding in these subjects was an early decrease in the 17-hydroxycorticosteroid level; this was followed by extreme fluctuations in these levels in subjects receiving repeated doses. During control periods these subjects had negligible diurnal fluctuations. In general,

decreases of steroid concentration occurred when the salicylate level was low; fluctuations and elevations when it was considerably elevated, usually above 25 mg. per cent. Moreover, subjects given low salicylate doses consistently showed a decrease in 17-hydroxycorticosteroid concentrations. The inconsistent increases in 17-hydroxycorticosteroid concentrations in response to single high salicylate doses, the consistent decreases in response to single low doses, and the marked fluctuations in responses to repeated doses suggest the possibility that salicylates cause both an increased peripheral utilization and an increased secretion of 17-hydroxycorticosteroids. Animal experiments designed to clarify the interpretation of these data are in progress.

THE ADRENAL RESPONSE TO BACTERIAL PYROGENS. *Kristen Eik-Nes and Leo T. Samuels,** Dept. of Biochemistry, Univ. of Utah College of Medicine, Salt Lake City, Utah.

The changes in concentration of 17-hydroxycorticosteroids have been studied in the peripheral blood of dogs and humans following the injection of various doses of partially purified bacterial pyrogen from Pseudomonas. The levels in the adrenal venous blood have also been followed in the dog.

Immediately after injection of the pyrogen the levels of cortical steroids rose. The concentration reached a peak at thirty-sixty minutes and then receded. The temperature change did not begin as soon as that of the steroids, and the most rapid rise was often after the steroid concentration had passed its peak. When ACTH was given at this time there was a further rise in the 17-hydroxycorticosteroids, associated with a temporary depression of the temperature rise. The same effect could be produced by intravenous injection of hydrocortisone or even by a second injection of pyrogen. In the latter case there was generally a rapid rise in temperature after the second rise in steroid concentration had passed its peak. It would seem that introduction of pyrogen leads to a discharge of adrenal steroids which depends on the immediate presence of the toxic compound and not on the febrile response.

A CORRELATION OF THE SPATIAL VECTORCARDIOGRAM WITH RIGHT VENTRICULAR HYPERTROPHY. *Stephen R. Elek,** *Bertram J. Allenstein, and George C. Griffith,** Dept. of Medicine, Univ. of Southern California, Los Angeles, Calif.

Using direct oscilloscopic vectorcardiography and the Duchosal-Sulzer cube arrangement, Grishman et al. have shown that the spatial vectocardiogram in right ventricular hypertrophy is shifted to the right anterior octant. Grishman has correlated the QRS sÊ loop with right ventricular pressure but only in congenital heart disease. We have correlated the spatial vectorcardiogram in congenital and acquired heart disease (mitral stenosis) with both mean right ventricular systolic ejection pressure and right ventricular work. We have also compared the vectorcardiogram with the electrocardiogram in both lesions.

Thirty-four patients (sixteen with mitral stenosis and eighteen with congenital heart disease) were chosen. The basis of selection was the presence of "isolated' right ventricular hypertrophy demonstrated by cardiac catheterization. Patients with clinical evidence of left ventricular hypertrophy were not included. Right ventricular work was determined by the formula of Gorlin; values above 1.0 Kg. M/min./sq.M. (hereinafter referred to as "units") were considered abnormal. In both lesions combined there were twenty-five patients with right ventricular work greater than 1.06 "units" and nine with right ventricular work less than 1.06 "units."

We have confirmed the increasing rightward deviation of the horizontal plane loop with right ventricular work above normal. The degree of rightward shift of the spatial vectorcardiogram was well correlated in twenty-two of the twenty-five patients with elevated right ventricular work. The data show that there is a closer correlation between the vectorcardiogram and right ventricular work than there is between the electrocardiogram and right ventricular work.

The electrocardiogram showed evidence of right ventricular hypertrophy in only thirteen of the twenty-five patients with right ventricular work above normal; nine of these patients had partial right bundle branch block. Vectorcardiographic evidence is offered that partial right bundle branch block does represent right ventricular hypertrophy. The data indicate that the vectorcardiogram clearly shows the existence of right ventricular hypertrophy while the electrocardiographic evidence of right ventricular hypertrophy is often obscured by the presence of partial right bundle branch block.

The vectorcardiogram, at least in congenital heart disease, may serve as a gross quantitative estimate of the degree of right ventricular hypertrophy and this can influence the preoperative decision.

DISTRIBUTION AND FATE OF INSULIN IN NORMALS AND IN SUBJECTS WITH VARIOUS LEVELS OF FUNCTION OF THE PITUITARY, THYROID, ADRENAL, PANCREAS AND LIVER. *Neil J. Elgee and Robert H. Williams,** Dept. of Medicine, Univ. of Washington School of Medicine, Seattle, Wash.

Highly purified crystalline insulin was labeled with I^{131} using the method of Ferrebee et al. (*Endocrinology*, 48: 277, 1951). The radioactivity could not be dialyzed away and did not move from the baseline on paper chromatograms using an acid-butanol solvent. The physiologic activity of the labeled insulin as measured by glucose uptake of the rat diaphragm was unimpaired. The material was given intravenously to patients with diabetes, cirrhosis, uremia, thyrotoxicosis, myxedema, Addison's disease and hyperinsulinism, and the radioactivity in blood and urine followed. Distribution and time studies in the rat were carried out following intravenous administration of the labeled insulin. In normal rats the radioactivity was very highly concentrated in kidney and liver, less in spleen and blood, and much less per unit mass in muscle, fat, thyroid, pancreas, testes, adrenals, pituitary and brain. No significant amount was found in the red blood cells. The effect of growth hormone, compound F, growth hormone plus compound F, thyroxine, insulin and the hyperglycemic factor on the distribution in normal, hypophysectomized and adrenalectomized rats and the effect of thyroidectomy and alloxan diabetes on the distribution of the radioactivity was studied.

The results of these experiments and some of their implications with respect to disorders of carbohydrate metabolism observed clinically will be discussed.

STUDY OF THE EFFECTS OF PHENYLBUTAZONE IN THE TREATMENT OF GOUT. *Ephraim P. Engleman,** *Marcus A. Krupp,** *Peter Forsham, A. Clark Griffin, Harold Johnson, Thomas Green and Alan Goldfien*, San Francisco Veterans Administration Hospital, Univ. of California School of Medicine, Stanford University Medical School, San Francisco, Calif.

Twenty-five male patients with acute gouty arthritis have been treated with phenylbutazone during the past year. In general the results have been excellent, with rapid, often dramatic, recovery. Ten of these patients had had recurrent gouty arthritis at regular intervals for years prior to the administration of phenylbutazone. Upon continuous treatment with adequate doses of the drug the cyclic recurrences of gout have not occurred, suggesting prophylactic value of the drug. The incidence of toxicity was high, necessitating cessation of the drug in one patient.

Four patients were subjects of careful study in an effort to discern the mechanism of action of phenylbutazone. The drug caused a striking decrease in the blood uric acid, despite failure to demonstrate an uricosuric effect. The urinary excretion of compound F-like substances in the urine was significantly decreased.

Preliminary studies have shown that phenylbutazone markedly enhances the P^{32} incorporation and turnover in liver tissue nucleic acid or nucleoprotein.

STUDIES ON MORPHOLOGIC ALTERATIONS ON HUMAN LYMPHOCYTES. *Jules A. Frank and Thomas F. Dougherty,** Dept. of Anatomy, Univ. of Utah, Salt Lake City, Utah.

Previous investigations in this laboratory on circulating lymphocytes of mice demonstrate that normal lymphocytes (numerically and morphologically) represent a balance between: (1) adrenocortical hormone influence (lymphopenia with morphologic alterations of pycnosis, cytoplasmic budding and karyorrhexis); and (2) a non-adrenocortically mediated influence (lymphocytosis and/or the morphologic alterations of hyalinization of cytoplasm and increased cytoplasmic-nuclear ratio).

Morphologically, circulating lymphocytes of stressed, adrenalectomized mice resemble the type II lymphocyte of Downey.

Observations on lymphocytes of normal subjects, normal subjects given ACTH and normal subjects given epinephrine were made and correlated with blood hydrocorticosteroid levels. Ten normal subjects given 15 mg. of ACTH intravenously exhibited a lymphopenia of normal lymphocytes at four hours anticipated by a rise in blood hydrocorticosteroids. Type II lymphocytes did not vary significantly from their control levels. Two normal subjects given 3.0 mg. epinephrine by infusion over four hours

exhibited a lymphocytosis of normal and type II lymphocytes at one hour and a return to normal values by the eighth hour. Following lymphocytosis the blood hydrocorticosteroids decreased to extremely low values.

Blood lymphocytes in several diseases were studied. In terminal cirrhosis high blood hydrocorticosteroids were accompanied by a lymphopenia of normal and type II lymphocytes. In infectious lymphocytosis normal and type II lymphocytes were equally represented. Infectious mononucleosis was accompanied by a lymphopenia of normal lymphocytes and a marked lymphocytosis of type II lymphocytes. Cortisone reversed the lymphocyte picture.

PRIMARY HYPERPARATHYROIDISM: FIVE CASES IN ONE FAMILY. *Richard N. Frohner.* (*Introduced by John A. Layne*), Dept. of Medicine, Great Falls Clinic, Great Falls, Mont.

Approximately 600 cases of primary hyperparathyroidism have been reported. The occurrence of the disease in the same family has been described only three times—once in two siblings, once in father and daughter, and once in cousins. This report describes a family of seven siblings of whom five had the disease. Renal function was good in all patients and none of the factors associated with secondary hyperparathyroidism was present. Each patient was operated upon; one had one adenoma, the others each had two adenomas. All were cured by operation. Of interest is the fact that the father, who died in 1945, had kyphosis, nocturia and polyuria for fifteen years and died in renal failure.

THE METABOLIC EFFECTS OF ACTH AND CORTISONE IN NON-TROPICAL SPRUE. *Joseph E. Giansiracusa,* T. L. Althausen,* Grant W. Liddle and Phillip Perloff*, Dept. of Medicine and the Metabolic Unit for Research in Arthritis and Allied Diseases, Univ. of California School of Medicine, San Francisco, Calif.

Four patients with non-tropical sprue were subjected to clinical and metabolic balance studies before and after treatment with ACTH and cortisone. The following data were obtained:

Influence of dietary fat intake on the fecal content of fat: The proportion of fat excreted in the feces of untreated patients varied inversely with the fat intake. Although this finding suggests more efficient absorption of fat with increased intake, our explanation is that the enteric excretion of endogenous fat furnishes a proportionately greater part of fecal fat during periods of low fat intake.

Clinical effects of administration of ACTH and cortisone: Our experience confirmed the favorable clinical response of patients with sprue to these hormones as previously reported by others.

Influence of ACTH and cortisone on fat absorption: (1) Unchanged and sometimes increased fecal excretion of fat on a constant fat intake was observed during treatment with these hormones, in spite of marked clinical improvement. (2) Characteristically flat vitamin A tolerance curves in sprue were markedly raised during administration of ACTH. These paradoxic observations suggest that ACTH may exert a dual effect in sprue, producing increased intestinal absorption of ingested fats and also increasing enteric excretion of endogenous fat.

Effects of fecal fat content on fecal nitrogen, phosphorus and calcium: No significant changes in these constituents of feces were observed. Administration of vitamin D to a patient with sprue complicated by osteomalacia produced a decrease in fecal phosphorus, a rise in serum phosphorus and a decrease in serum alkaline phosphatase.

ESTIMATION OF DIFFUSION CONSTANTS OF PROTEINS BY MEANS OF AGAR GEL CONTAINING ANTIBODY. *B. V. Jager,* Emil Smith and D. M. Brown*, Dept. of Internal Medicine, College of Medicine, Univ. of Utah, Salt Lake City, Utah.

There is growing interest in studies relating to the diffusion of antigenic substances into antibody contained in agar. The rate of diffusion is indicated by the advancing zone of precipitate formation resulting from interaction of antigen and antibody. Such technics afford useful evidence for the homogeneity or heterogeneity of antigen-antibody systems.

Certain variables which influence the sensitivity of this sytem will be discussed with reference to the limitation of this method for detecting multiple antigen-antibody components.

The equations developed by Adair for the diffusion of low molecular weight electrolytes into gels have been found to be applicable to the antigen-antibody system. The diffusion constants for egg albumin, bovine serum albumin and human globulin are in reasonable agreement (± 10 per cent) with those obtained by other methods.

USE OF CORTISONE OR ACTH DURING RAPID DESENSITIZATION OF ALLERGIC PATIENTS. *Edmund L. Keeney,* Harry A. Weiss and Edward Mears*, Allergy Clinic and Dept. of Medicine, U. S. Naval Hospital, San Diego, Calif.

A patient with idiopathic diabetes insipidus hypersensitive to posterior pituitary extracts and pitressin, and a patient with diabetes mellitus hypersensitive to unmodified globin, NPN, and protamine zinc insulins were rapidly desensitized with pitressin tannate in oil and unmodified insulin, respectively. During the period of desensitization symptoms of hypersensitivity were controlled by administering concomitantly cortisone orally in dosages of 100 mg. daily.

The patient with diabetes insipidus received a gradual increase in dosage of pitressin tannate in oil four times daily over a period of six days. When the desired therapeutic dosage of 0.5 cc. four times daily was attained, this was modified to 1.0 cc. twice daily and the cortisone gradually withdrawn over the following six days. The previous allergic manifestations of urticaria and asthma did not reappear and the patient has continued with pitressin tannate in oil therapy for the past two years without the complication of allergic reactions.

The patient with diabetes mellitus gave a history of allergy to insulin and following a test dose of 1 unit of unmodified insulin immediately developed symptoms of anaphylactic hypersensitivity characterized by generalized urticaria, tightness in the chest and a drop in the blood pressure. During a ten-day period while cortisone was given orally in doses of 50 mg. twice daily he gradually received increasing doses of insulin until a therapeutic level of 35 units daily was attained. The cortisone was discontinued and the patient has been able to receive a daily dose of 35 units of unmodified insulin for the past year without reappearance of hypersensitivity.

The results obtained in the treatment of these two patients indicated that cortisone does not impede the mechanisms of desensitization but at the same time does shield the allergic patient from manifestations of hypersensitivity during a period of rapid desensitization. The possibility arose that patients with bronchial asthma, hay fever and allergic intrinsic eczema hypersensitive to pollens and environmental antigens might be favorably and similarly managed.

Nine patients with severe chronic bronchial asthma and allergic rhinitis, four patients with chronic allergic intrinsic eczema, one patient with chronic bronchial asthma and chronic allergic intrinsic eczema, and one patient with chronic bronchial asthma received rapid desensitization while under treatment at the same time with 10–30 I. U. of ACTH daily. The periods of rapid desensitization varied from nine to twenty-nine days. As soon as the optimal concentration of antigen for each patient was attained the ACTH was discontinued and the patient put on a maintenance dose of antigen, once or twice weekly. The results of treatment were excellent in ten, good in two, fair in two, and poor in one of the patients. These fifteen patients have now been under observation for from one to two years.

FURTHER STUDIES IN LIPID AND CARBOHYDRATE METABOLISM IN DIABETIC SUBJECTS. *Laurance W. Kinsell,* George D. Michaels, and Harry E. Balch*, Alameda County Hosp., Oakland, Calif.

In previous reports from this laboratory it has been observed that administration of corticotropin and of 11-oxygenated steroid hormones to diabetic patients resulted in D/N ratios compatible with the concept of neoglucogenesis from fat, and rapid development of insulin resistance to such a degree as to result in premature curtailment of the study. It was also noted that administration of significant amounts of potassium salts appeared to diminish the steroid hormone-induced insulin resistance under such circumstances.

In more recent studies in diabetic patients receiving chemically constant formula diets containing fat and protein but no carbohydrate, and supplemented with essential vitamins and with varying amounts of sodium, potassium and other ions, it has been found that administration of very large amounts of potassium, and of other ions in sufficient quantity to prevent major depletion of such ions, completely prevented the development of insulin resistance. In a patient maintained on such a program D/N ratios in excess of 6.25 have been observed for continuous periods of more than twenty-four hours, and for total periods of sixty-four hours. D/N ratios in excess of 10.0 have been obtained for ten-hour periods. It seems probable that such D/N values could be maintained indefinitely but for the practical difficulties attendant upon very prolonged hyperglycemia.

It is concluded that administration of ade-

quate amounts of corticotropin or of cortisone to diabetic patients on chemically constant, carbohydrate-free diets, under suitable conditions, resulted in D/N ratios far in excess of 6.25. In other words, urinary glucose far exceeds the amount of carbohydrate which could be accounted for if 100 per cent of the catabolized protein were changed to carbohydrate. One must therefore conclude that cortisone-like steroids have the property of accelerating neoglucogenesis from fat. It may also be inferred that potassium depletion is an essential component of steroid hormone-induced diabetogenesis in general, and insulin resistance in particular. Prevention of such potassium depletion favorably modifies the diabetogenic effects and appears to inhibit completely the development of insulin resistance. Very large amounts of potassium may be required to maintain such patients in positive balance.

SERIAL LIPOPROTEIN STUDIES IN A PATIENT WITH XANTHOMATOSIS SECONDARY TO ACROMEGALY AND UNCONTROLLED DIABETES. *Felix O. Kolb, John W. Gofman, Oliver de Lalla and William L. Epstein* (*Introduced by Jonah G. Li*), Div. of Medicine and Medical Physics and the Metabolic Unit, Univ. of California School of Medicine, San Francisco, Calif.

The xanthomatoses comprise a heterogeneous group of striking diseases differentiated largely on the basis of etiology and gross appearance of lesions. The group of fixed tissue xanthomatoses, presumably due to a defect in the reticuloendothelial system, shows normal serum lipid levels. Hence this group is readily differentiated from the larger group of xanthomatoses in which the lipid content is abnormal. Separation of the diseases in the latter group has been more difficult because of the great variations in cholesterol and phospholipid levels. Clinical terms, such as "tuberous" or "eruptive," which describe localization or rate of appearance of lesions rather than their specific chemical abnormalities, have been used. The introduction of the ultracentrifuge has made it possible to define the specific defect in lipid transport in these syndromes, and a classification based on this concept has been proposed.

We had the opportunity to study a patient with acromegaly and uncontrolled diabetes in acidosis who had extensive xanthoma formation. Clinically, the lesions were indistinguishable from the "tuberous" and "plane" forms; a few more recent lesions resembled the "eruptive" forms. Serial lipoprotein studies showed a dramatic change from the markedly abnormal pattern of the serum on entry toward that of the controlled state after treatment of the diabetes and acromegaly. These changes were correlated with disappearance of the lesions. The clinical implications of these observations will be discussed.

CLINICAL ESTIMATION OF THE BLOOD PRESSURE IN MINUTE VESSELS OF THE HUMAN SKIN BY THE METHOD OF ELEVATION AND REACTIVE HYPEREMIA. II. EFFECT OF SYMPATHECTOMY. *Frank H. Leeds,* Norman E. Freeman* and Rutherford S. Gilfillan*, Vascular Research Laboratory, Franklin Hospital, and the Dept. of Surgery, Univ. of California Medical School, San Francisco, Calif.

The blood pressure in the minute vessels of the skin of the foot has been estimated by a method of elevation and reactive hyperemia. This consists in raising the feet to 65 cm. above the auricle and then applying occlusive cuffs for five minutes. If within one minute after release of the cuffs reactive hyperemia does not appear the feet are gradually lowered until flushing takes place and this level is noted. Previous studies in this laboratory have shown a prognostic relationship between this level and the healing of necrotic lesions of the foot.

The present report deals with a group of thirty patients in whom the height at which reactive hyperemia appears has been measured before and after lumbar sympathectomy. In the majority of cases the level remains the same or rises. Two patients showed a drop in the height at which reactive hyperemia appears.

Reactive hyperemia has been shown to depend upon the accumulation of local metabolites during the period of ischemia. It is supposed to be independent of the nervous system but is dependent on the arterial pressure in the extremity. Our findings will be discussed with reference to these postulates.

CHROMATOGRAPHIC SEPARATION OF A CORTICOID FRACTION CONTAINING SODIUM-RETAINING ACTIVITY FROM THE URINE OF PATIENTS WITH EDEMA. *John A. Luetscher, Jr.* and Ben B. Johnson*, Dept. of Medicine, Stanford Univ. School of Medicine, San Francisco, Calif.

Increased sodium-retaining activity has been demonstrated by bio-assay of the corticoid fraction of urine of certain patients with edema

and of normal men on low-sodium diets. In patients with the nephrotic syndrome a reduction in the level of sodium-retaining activity occurs when diuresis follows treatment.

Urine extracts have been chromatographed by the method of Zaffaroni and Burton, using the following crystalline adrenal cortical steroids as standards: Kendall's A, B, E, F; Reichstein's S; and desoxycorticosterone. The measured sodium-retaining activity of the crude extract can be recovered from the chromatographic fraction moving with the same rate as cortisone. Amounts of cortisone corresponding to the chemically determined corticoids in this fraction have no sodium-retaining activity in the bioassay used.

When the sodium-retaining activity of the urine extract is decreased during diuresis following administration of ACTH or cortisone in the nephrotic syndrome, there is a corresponding decrease in the activity of the chromatographic fraction moving with cortisone, which is not necessarily dependent on the increased quantity of cortisone excreted. During diuresis there may be an increased quantity of other corticoid fractions which promote sodium excretion in the assay used.

It is concluded that none of the known biologically active corticosteroids accounts for the sodium-retaining activity measured in urine extracts. The chromatographic behavior of the unidentified active substance resembles that of the highly active mineralocorticoid reported by Grundy, Simpson, Bush and Tait in beef adrenal extract and in mammalian adrenal vein blood.

PHYSIOLOGIC EFFECTS OF CONDENSER DISCHARGES WITH APPLICATION TO VENTRICULAR DEFIBRILLATION. *R. Stuart Mackay and Sanford E. Leeds,** Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, in conjunction with Dept. of Electrical Engineering, Univ. of California, Berkeley, Calif.

For use in surgical emergencies where valuable time is required to expose a fibrillating heart, and as the only possibility in accidental electrocution, closed chest defibrillation was investigated. The required momentary current of many amperes at several thousand volts can most practically be supplied by the sudden discharge of a condenser that has slowly stored this energy. The first experiments on dogs showed that 2 to 12 microfarad condensers, charged to from 500 to 4,000 volts, can be discharged through the chest without apparently producing ill effects aside from superficial burns of the skin. Ventricular fibrillation was never produced and shocks through the spinal cord did not produce paraplegia.

These intense discharges stopped fibrillation caused by a low voltage shock. If one plots on log paper the defibrillation threshold voltage against the condenser capacity, the points fall on a line of slope two which indicates that in this range the heart responds to the energy ($\frac{1}{2}CV^2$) stored in the condenser rather than, for example, the charge (CV); i.e., it responds to joules not coulombs. The required energy is less for small dogs. It is almost halved by converting the unidirectional current into an alternating discharge through placing inductance in series with one electrode. It was observed during many experiments that successive defibrillations were easier and a lower fibrillating voltage was required, indicating that progressive changes occur.

INFLUENCE OF NORMAL AND TOXEMIC PREGNANCY UPON RENAL CLEARANCE OF INULIN AND HISTIDINE. *Ernest W. Page,** *William Dignam, Mary Beth Glendenning and Harold Harper*, Dept. of Obstetrics and Gynecology, Univ. of California School of Medicine, and Dept. of Biology, Univ. of San Francisco, San Francisco, Calif.

Simultaneous renal clearance tests with inulin and histidine were performed by the constant infusion technic on volunteer normal subjects eight months pregnant and upon selected pregnant patients with pre-eclampsia or essential hypertension. The identical tests were repeated on the same subjects from two to six weeks after delivery. Plasma and urinary concentrations of amino acids were determined microbiologically.

The most striking finding in normal pregnancy is a doubling of the glomerular filtration rate. Quantitatively speaking, this appears to be the major factor responsible for the characteristic histidinuria of normal pregnancy. Addition of arginine to the infusion did not alter the histidine clearance. Two other factors contribute to the histidinuria, however. Since the ratio C histidine/C inulin increased in each case as the result of pregnancy, it is evident that there is a diminished tubular reabsorption of histidine at this time. Secondly, and in contrast to inulin and arginine, it was noted that the

plasma concentrations achieved by constant infusion of the same quantity of histidine were just as high or higher during pregnancy as in the puerperium, despite the greater volume of distribution. This suggests a diminished rate of metabolism for histidine during human pregnancy.

The decrease of histidinuria in pre-eclampsia is primarily due to the markedly lowered glomerular filtration rates found in that disease.

PARADOXIC HYPERGLYCEMIA IN DIABETIC PATIENTS TREATED WITH INSULIN. *Gerald T. Perkoff and Frank H. Tyler,** Dept. of Internal Medicine, College of Medicine, Univ. of Utah, Salt Lake City, Utah.

We have observed seven "brittle" diabetic patients in whom the administration of increasing amounts of insulin was associated with increased hyperglycemia and glycosuria. Reducing the insulin dose resulted in return of the blood sugar toward normal and in decrease in glycosuria. Two patients studied in detail exhibited a constant pattern of cyclic glycosuria with days of massive glycosuria following a single day of minimal glucose excretion. The cyclic nature of the glycosuria was apparent in the fractional urine collections for a single day as well. Judicious reduction in insulin dose eliminated this unusual pattern of glycosuria at the same time that the total glycosuria was reduced and the regulation of the diabetes improved.

This "paradoxic hyperglycemia" has not generally been recognized because comprehensive, clinical data concerning this type of patient have not been published in readily available journals. The progressive deterioration of diabetic regulation in these patients is a clinical manifestation of the hyperglycemic response to hypoglycemia. Hypoglycemia not necessarily associated with clinical symptoms is followed by a period of excessive hyperglycemia and glycosuria. This response is probably related to substances such as epinephrine, adrenal corticosteroids and others, which are "insulin-antagonistic" in the sense that they act to increase the blood sugar.

Studies of clinical technic for recognizing those diabetic patients, whose poor regulation is due to the administration of too much rather than too little insulin, will be described.

SERUM HEMOLYSIN FOR ERYTHROCYTES COATED WITH NONSPECIES-SPECIFIC BACTERIAL PRODUCTS IN HEALTH AND IN VARIOUS DISEASES. *Lowell A. Rantz,** Dept. of Medicine, Stanford Univ. School of Medicine, San Francisco, Calif.

A nonspecies-specific substance is present in culture filtrates of most gram-positive bacteria which prepares erythrocytes for hemolysis in the presence of complement and certain human sera. The serum hemolysin responsible for this reaction has been extensively studied. It possesses the characteristics of a true antibody. It is adsorbed on the coated red cells and the reaction requires complement. Titers are higher and comparable to those found in the mother of certain children at birth and wane rapidly during the first half year. A progressive increase occurs in healthy persons during life.

The actual antigen responsible for this antibody response in human beings is unknown. Mean concentrations are high in acute rheumatic fever, periarteritis nodosa, disseminated lupus erythematosis, scleroderma and acquired hemolytic anemia. They are normal or low in rheumatoid arthritis, acute nephritis and nephrosis. It is probable that this antigen-antibody system is not intimately related to the pathogenesis of these disorders. The presence of these abnormal antibody patterns may well reflect an immunologic hyper-reactivity of persons who develop them. It is believed that these observations add further weight to the hypothesis that inappropriate immunologic reactions are involved in the causation of this group of diseases.

THE RENAL GLOMERULUS IN HEALTH AND DISEASE. *James F. Rinehart,* Marilyn G. Farquhar, Haw Chan Jung and S. K. Abul-Haj*, Univ. of California School of Medicine, San Francisco, Calif.

A further study has been made of normal and pathologic renal glomeruli, utilizing improved histologic technics which serve to differentiate epithelial and endothelial components. The structure of the normal renal glomerulus has also been studied by electron microscopy.

The basement membrane is considered to be a differentiated product of the endothelial cell. Most intimately associated with the endothelial basement membrane is the cytoplasmic secretion or product of the surfacing epithelial cells. The cytoplasmic product of the epithelial cells has staining properties of a mucopolysaccharide or mucoprotein. This substance shows multiple points of attachment to the endothelial mem-

brane and is thinly spread over the entire surface. Evidence derived chiefly from electron microscopy indicates that the endothelial membrane is "porous" and it appears that the epithelial mucoid substance penetrates the endothelial membrane, somewhat analogous to the cement lines in tile. Changes which are considered to be the basic alterations in structure occurring in glomerular disease are presented.

In glomerulonephritis endothelial cell proliferation is associated with reduplication of the endothelial basement membrane. Epithelial proliferation with mucoid formation is a variable manifestation. In eclampsia there is evident contraction of glomerular loops with thickening of the endothelial membrane, relative ischemia and not infrequently a tubular lesion resembling "lower nephron" nephrosis. A peculiar hyaline thickening and staining alteration of the basement membrane may be seen in acute disseminated lupus. Endothelial cell proliferation may occur also in this condition. Mild basement membrane thickening is encountered in essential hypertension. In the malignant phase this may be associated with arteriolar necrosis and thrombosis in arterioles and some glomerular loops. In diabetes the Kimmelstiel-Wilson lesion is associated with prominent thickening of the endothelial basement membrane particularly of the axial portions of the loops.

Collagen is essentially absent in normal or abnormal glomeruli.

THE CHOLATE/CHOLESTEROL RELATIONSHIP IN CLINICAL AND EXPERIMENTAL NEPHROSIS. *Ray H. Rosenman, Meyer Friedman,* and Sanford O. Byers,** Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

Recent studies from this laboratory have shown a unique relationship between cholic acid and cholesterol. This relationship was studied in the nephrotic syndrome. (1) The serum cholates of fifteen nephrotic, hypercholesteremic patients varied from 10 to 44 mg./100 cc. compared to a range of 2 to 7 mg./100 cc. in twenty-five normal persons. (2) A nephrotic state was induced in rats by injection of rabbit anti-rat kidney serum. The average plasma cholate rose from 5.9 mg./100 cc. to 23.1 mg./100 cc. in twenty-two nephrotic rats. Simultaneously, their average plasma cholesterol rose from 71 to 460 mg./100 cc. Thus "hypercholatemia" was observed whenever hypercholesteremia was found, in both clinical and experimental nephrosis. (3) The ability of nephrotic rats to eliminate excess cholate from their blood was then tested periodically following the intravenous injection of a standard dose of cholate. It was found that excess injected cholate disappeared from the blood of nephrotic rats more slowly than from control animals. (4) As shown by others, we have found that the early maximum rise of plasma cholesterol following onset of the nephrotic state in rats thereafter progressively decreases. When cholate was fed to half of a group of nephrotic rats, it prevented the fall of plasma cholesterol occurring in the untreated group. (5) The biliary cholesterol concentration has been shown in this laboratory to be a reliable index of rate of hepatic synthesis of cholesterol. This technic was used in nephrotic rats and it was found that the rate of synthesis apparently was moderately decreased.

These studies suggest that nephrotic hypercholesteremia is related to elevated plasma cholate levels invariably also present. This hypothesis is strengthened by studies in which we found that hypercholatemia is present in a variety of clinical and experimental hypercholesteremic states. Furthermore, hypercholesteremia develops whenever hypercholatemia is induced by injection of cholate. The mechanism by which cholate may produce hypercholesteremia will be discussed.

EFFECT OF OUABAIN UPON MAXIMUM PERFORMANCE OF NORMAL DOG'S HEART. *Arthur Selzer,* Russel H. Lee, Walter H. Goggans and Frank Gerbode*, Depts. of Medicine and Surgery, Stanford Univ., San Francisco, Calif.

A method has been devised by which the maximum performance of the dog's heart can be accurately assessed in acute experiments by means of graded quantitative constriction of the main pulmonary artery: Simultaneous pressure curves were recorded from the right ventricle and the femoral artery. The pulmonary artery was constricted in stages until intolerance of constriction was evidenced by (1) fall in right ventricular systolic pressure from its highest level with increase in diastolic pressure; and (2) abrupt fall in systemic pressure indicative of inadequate output.

Such experiments were performed in fifteen dogs by producing at least three periods of constriction in each animal and then repeating the procedure after an injection of a therapeutic dose of ouabain. Thus in each dog the maximum

tolerance of constriction of the pulmonary artery was compared before and after the administration of ouabain. In two-thirds of the animals ouabain had a measurable effect upon the heart in permitting tolerance of more constriction and postponing the physiologic fatigue from overloading. It is concluded therefore that ouabain exerts a favorable effect upon the dog's normal heart under stress.

ROLE OF THYROTROPHIC HORMONE IN THE PATHOGENESIS OF EXOPHTHALMOS. *Benjamin Simkin,* Paul Starr* and Charles Hancock*, Dept. of Medicine, Univ. of Southern California School of Medicine, Los Angeles, Calif.

Last year we presented data showing that thyroid-stimulating doses of thyrotrophic hormone (TSH) do not produce exophthalmos in man. Further observations indicate that relatively much larger doses of the same preparation of TSH administered to the guinea pig produces clear-cut exophthalmos in this species.

Serum TSH assays were made in twenty patients exhibiting exophthalmos, with the following results (normal eye measurements range from 10 to 17 mm.).

Thyroid Status	No. of Patients	Exophthalmometer Readings (mm.)		Increase MACH (μ)
		OD	OS	
Euthyroid.....	6	21.23	21.61	+0.15 (no serum TSH)
Hyperthyroid...	8	20.25	20.76	+0.13 (no serum TSH)
Hypothyroid...	6	20.54	20.56	+0.82 (serum TSH present)

The serum TSH assay results in these patients with exophthalmos are similar to those obtained in patients with the corresponding thyroid states but without exophthalmos (previously reported by us). It may be concluded that serum TSH levels in patients with exophthalmos are dependent on their thyroid status rather than the presence or absence of exophthalmos.

Another study concerned the distribution of TSH labelled with radioactive iodine in the orbital tissues of the thyroidectomized rat following intracardiac injection of the labelled hormone in this species. Control observations were made with labelled serum albumin. It was found that there is no selective localization of TSH in the retro-orbital fat or extraocular muscles of the thyroidectomized rat.

All of the observations cited above are consistent with the theory that TSH *per se* is not the factor that causes exophthalmos.

TURNER'S SYNDROME IN TWO MALES AND ONE FEMALE WITH CONGENITAL HEART DISEASE. *Frank H. Tyler,* Hans H. Hecht* and Avery A. Sandberg*, Dept. of Internal Medicine, College of Medicine, Univ. of Utah, Salt Lake City, Utah.

We have observed three patients with Turner's syndrome during the past two years who presented certain features which contrast with previous reports of this disorder. Specifically, two of the patients were males and each of the patients had congenital heart disease which on complete study proved to be other than coarctation of the aorta.

Patient	Sex	Age	Gonads	Heart
A. S.	M	11	Infantile testis	Interatrial septal defect
C. S.	F	7	Ovarian agenesis	Interventricular septal defect
W. F.	M	2	Undescended testes	Pulmonary stenosis, aberrant pulmonary vein, patent foramen ovale

EFFECT IN PLASMA THROMBOPLASTIN COMPONENT (PTC) DEFICIENCY OF INTRAVENOUS ADMINISTRATION OF PLASMA FRACTION IV. *Sidney G. White, Paul M. Aggeler* and Byron E. Emery*, Dept. of Medicine, Univ. of California School of Medicine, San Francisco, Calif., and the Cutter Laboratories, Berkeley, Calif.

Plasma thromboplastin component (PTC) deficiency, which resembles hemophilia, does not respond to Fraction I of Cohn. An investigation was made of the various Cohn fractions *in vitro* by testing their effect on the PTC deficient patient's defective prothrombin utilization. The PTC potency of Fractions II + III, IV and IV-1 was high; of I and V slight; and of II and IV-4, none. Since Fraction III contained thrombin it could not be separately assayed for PTC nor administered intravenously. Although Fraction IV-1 was potent its solubility was too poor for intravenous use.

A preparation of Fraction IV for intravenous use was made as follows: an 11 per cent concentration of the fresh fraction was mixed in a

Waring blender, passed through a sterilizing porcelain filter and frozen. After filtration it contained 9.2 per cent total solids, 6.5 per cent protein, 190 units prothrombin per cc. and 69 per cent of the proconvertin of an equivalent volume of plasma. Tests for sterility, pyrogenicity, toxicity and vasodepressor effects in rabbits were negative.

In a typical experiment, before administration of the fraction the patient's coagulation time was twenty-two minutes and serum prothrombin 100 per cent. At fifteen minutes, four hours, twenty-four hours and four days after administration of 85 cc. of the fraction the values were: twelve minutes and 17 per cent, twelve minutes and 24 per cent, sixteen minutes and 45 per cent, and twenty-three minutes and 88 per cent. These results compare favorably with those found after the administration of a comparable amount of Fraction I in hemophilia.

THE NATURE OF THE ACTION OF INSULIN. *Arne N. Wick* and Douglas R. Drury,** The Scripps Metabolic Clinic, La Jolla, California and the Univ. of Southern California, Los Angeles, Calif.

Recent work has indicated that insulin exerts its action at the surface of the cell, promoting there the entry of glucose into the cell. According to this view the apparent results of insulin administration—increased oxidation and storage of glucose—follow secondarily the increase in amount of glucose that has entered the cells. It has been suggested that this theory might be tested by seeing whether other hexoses, similar to glucose but not oxidized or otherwise metabolized even if they enter the cell, were transferred intracellularly at increased rates as a result of insulin action. To this end we have studied the metabolic reactions to insulin of several compounds closely related to glucose. Sorbitol, gluconic acid and fructose distribute in the body in the extracellular space only and do not enter the cell to more than an insignificant degree. On the other hand, galactose and mannose will enter the cells in relatively large amounts as a result of insulin action. These hexoses are not metabolized to any great extent after entry into the cell.

These findings support the view that insulin acts by promoting the transfer of glucose into the cell. This action is relatively but not absolutely specific—carbohydrates with a chemical structure closely approximating that of glucose being acted on in the same way.

SIGNIFICANCE OF THE INDUCED DIGITAL VASOCONSTRICTOR REFLEXES. *Travis Winsor,** Hosp. of Good Samaritan, Los Angeles, Calif.

The induced digital vasoconstrictive reflexes are involuntary vasoconstrictor reactions which may follow stimulation of sensory organs or may arise from other sources such as the cerebral cortex. This report deals with an analysis of these reactions which follow certain stimuli (inspiration, expiration, anticipation, cold, tickle, pain, a startling sound and a startling light). Five hundred reflexes were studied among 250 subjects to determine the nerve pathways involved and the clinical significance of these reactions. Although eight different stimuli were employed, the reaction was qualitatively but not quantitatively similar. The reaction to sound took place an average of 3.2 seconds after stimulation and was complete usually in 45 seconds. The reaction consisted of a decrease in the total volume and volume pulsation of the digit and was associated ordinarily with sweating, as shown by the simultaneously recorded psychogalvanogram. The reflex could be inhibited voluntarily by mental effort and could be fatigued by repeated stimulation for two to four minutes. The magnitude of the reflex was relative to the magnitude of the stimulus. The reflexes could be abolished by lesions in the receptor organ, afferent pathways or in the cerebrum, and by novocain injected into the sympathetic vertebral ganglia or peripheral nerves. Tetraethyl ammonium chloride, dimethyl, di-ethyl piperidinium chloride, the hydrogenated alkaloids of ergot and benzylimidazoline parenterally blocked these reflexes. Oral whiskey, 60 cc., failed to block the reflexes.

Knowledge of these reactions aided in determining the extent of organic arterial disease present in twenty cases. The presence of a deep reflex signified a good result following lumbar sympathectomy in twenty cases. The simultaneous recording of this reflex from a digit of each extremity assisted in localizing obstructive lesions in the sympathetic nervous system in two patients. The presence of this reflex before and its absence soon after lumbar sympathectomy provided a means of determining the completeness of lumbar sympathectomy in thirty patients and repeated determinations at intervals of months provided a means of determining the rate of regrowth of sympathetic nerves after surgery in thirty cases.

Case Reports

Reabsorptive Hyperchloremic Acidosis Following Ureterosigmoidostomy*

Report of a Severe Case Showing Disturbed Carbohydrate Metabolism

CHARLES E. WILDER, M.D.† *and* ROBERT T. COTTON, M.D.‡
Topeka, Kansas

In April, 1950, a twenty-six year old white farmer was subjected to cystectomy, left nephrectomy and right ureterosigmoidostomy following the discovery of an infiltrating, grade IV, transitional cell carcinoma of the bladder and an obstructing papilloma of the left ureter with secondary left hydronephrosis and pyelonephritis. Pathologic examination of a regional lymph node found at surgery revealed secondary carcinoma. Following surgery he made a gradual recovery, complicated only by a febrile episode accompanied by a rise in serum non-protein nitrogen to 60 mg. per cent. However, he did sustain a considerable loss of weight which was not subsequently regained. During the next fourteen months he felt well but noted that he drank unusually large amounts of water and had a chronically dry skin. Exertional dyspnea, weakness and moderate anorexia were also experienced at times.

On January 12, 1952, he developed severe, generalized abdominal pain accompanied by anorexia, chills and fever. His urinary output increased, as evidenced by fluid bowel movements ten times daily instead of his usual four. There was a single emesis. Upon admission to the Winter Veterans Administration Hospital, Topeka, Kansas, on January 16th, physical examination showed a moderately undernourished young male with warm, very dry skin. Blood pressure was 118 mm. Hg systolic and 75 mm. diastolic. The pulse rate was 88 per minute and the temperature was 100°F. There was moderate abdominal splinting with generalized abdominal tenderness and rebound tenderness, most marked on the right. Bowel sounds were normal. Tenderness was elicited over the right costovertebral angle.

Admission laboratory studies revealed 16,700 leukocytes with 88 per cent neutrophils, 6 per cent lymphocytes, 6 per cent monocytes, 4,040,000 erythrocytes, 11.5 gm. hemoglobin, a hematocrit of 40 per cent, a corrected Wintrobe sedimentation rate of 25 mm. per hour, and a blood urea nitrogen of 47 mg. per cent. Although only a small amount of dye could be visualized, the right kidney appeared normal on intravenous pyelography.

The patient was treated at bed rest with procaine penicillin and sulfadiazine on the assumption that he was suffering from pyelonephritis. The temperature and pulse rate were normal on the day after admission. Within five days the total leukocyte count, differential and sedimentation rate were also normal. The patient had improved symptomatically, although there were mild periodic complaints of chilliness, nausea especially in the evening, and occasional emesis. All symptoms subsided for about one week but on the twelfth day of hospitalization he again complained of extreme chilliness despite a normal temperature. This persisted for several days during which a marked increase in frequency and fluidity of bowel evacuations occurred. On the fifteenth day hyperpnea was noted. Hysterical hyperventilation and metabolic acidosis were considered. The serum carbon dioxide combining power on the sixteenth day was 20 volumes per cent (9.1 mEq./L.) and the serum chlorides 114 mEq./L. 1,000 cc. of $\frac{1}{6}$ molar lactate solution was administered intravenously and the patient given 15 gm. of sodium bi-

* From the Medical Service, Winter Veterans Administration Hospital, Topeka, Kan.
† Now Lt. (jg) USNR, Dispensary, Marine Air Station, Edenton, N. C.
‡ Now Capt. USAF, Nellis Air Force Base, Las Vegas, Nev.

carbonate five times daily. On the next day the serum carbon dioxide combining power was 59 volumes per cent (27 mEq./L.). The blood glucose on the seventeenth day of hospitalization was 133 mg. per cent. On the eighteenth day the patient's temperature again rose to 100°F. but subsided promptly with gantrisin® treatment. The remainder of his hospitalization was uneventful. The blood urea nitrogen fell to 33 mg. per cent and, although he remained moderately anemic, he was discharged asymptomatic on the twenty-ninth hospital day with a diagnosis of recurrent pyelonephritis.

The patient was readmitted on April 1, 1952, about ten weeks later, because of respiratory distress of one day's duration. He had felt well and had been able to do small chores about the farm until two weeks before when he felt feverish and noted a transient aching in the right flank. He took aureomycin for a few days with complete relief, but on the day before admission he felt chilly, drank large quantities of water, passed abundant fluid by rectum and began to feel unable to get enough air into his lungs. The latter symptom progressed until it interfered with the mastication and swallowing of food.

On examination he was found to be hyperventilating markedly, shivering, and asking frequently for more blankets and for water. Although appearing drowsy and lethargic, he answered questions fully and intelligently. His breath was not uremic; nor did it carry an odor of acetone. The Chvostek and Trousseau signs were negative. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Rectal temperature was 98.6°F., respiratory rate was 40 per minute and pulse rate was 84 per minute. The tongue was moist. Moderate right costovertebral angle tenderness was present.

Admission laboratory work revealed 14,200 leukocytes with 88 per cent neutrophils, five of these being stabs, 9 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils, 3,870,000 erythrocytes, 11.9 gm. of hemoglobin, a corrected sedimentation rate of 23 mm. per hour, a serum carbon dioxide combining power of 21 volumes per cent (9.5 mEq./L.), and a blood urea nitrogen of 52 mg. per cent. Blood uric acid values were consistently within normal limits. Blood creatinine levels were normal except for the single value of 3.0 mg. per cent on the forty-second hospital day.

On the day of admission the patient was heavily sedated in an attempt to rule out hysterical hyperventilation but, although the respirations decreased in rate, they remained very deep. He was given 2 L. of ⅙ molar sodium lactate and was started on a regimen of 1 gm. of sodium bicarbonate four times daily. Fluids were given by mouth as desired and were taken in large quantities. He was also given aureomycin and gantrisin. His temperature, which rose to 101°F. on the day of admission, returned to normal within forty-eight hours and remained subnormal (96°F. to 98°F.) during the remainder of his hospital course. On the second hospital day the respiratory rate was less rapid (32 per minute) and respirations were more shallow, although the carbon dioxide combining power was still 29 volumes per cent (13 mEq./L.) and the serum chlorides 119 mEq./L. (Fig. 1.)

The patient felt better and, for the next twelve days, he was cheerful and was up and about the ward without complaint. On the fifth, eighth and fifteenth hospital days he received 500 cc. of whole blood, with some improvement in hemoglobin and red blood cell count. On the fifteenth day the carbon dioxide combining power was 14 volumes per cent (6.4 mEq./L.) and the serum chlorides were 122 mEq./L. On this day he refused breakfast, complained of chilliness, remained in bed all day under blankets, appeared drowsy and listless, had frequent fluid bowel evacuations, drank large amounts of water, evidenced salt hunger and again began to hyperventilate. In addition to 500 cc. of whole blood, he received a L. of ⅙ molar sodium lactate solution and his sodium bicarbonate dosage was increased to 2 gm. four times daily. Blood chemistry values were essentially unchanged the next day although he then complained only of weakness, anorexia and moderate nausea. On that day sigmoidoscopic examination was performed and clear urine was obtained by aspiration near the entrance of the ureter. The specimen gave negative tests for sugar, acetone, diacetic acid and albumin and contained 60 mEq./L. of sodium chloride, 502 mg. per cent of urea and 2 to 6 leukocytes per high power field. The specific gravity was 1.004 and the pH 6.5. A fasting blood glucose on the seventeenth day was 136 mg. per cent. During the next week he was frequently nauseated and sometimes vomited in the evening, this appearing to be relieved by bedtime snacks. Throughout the remainder of his hospitaliza-

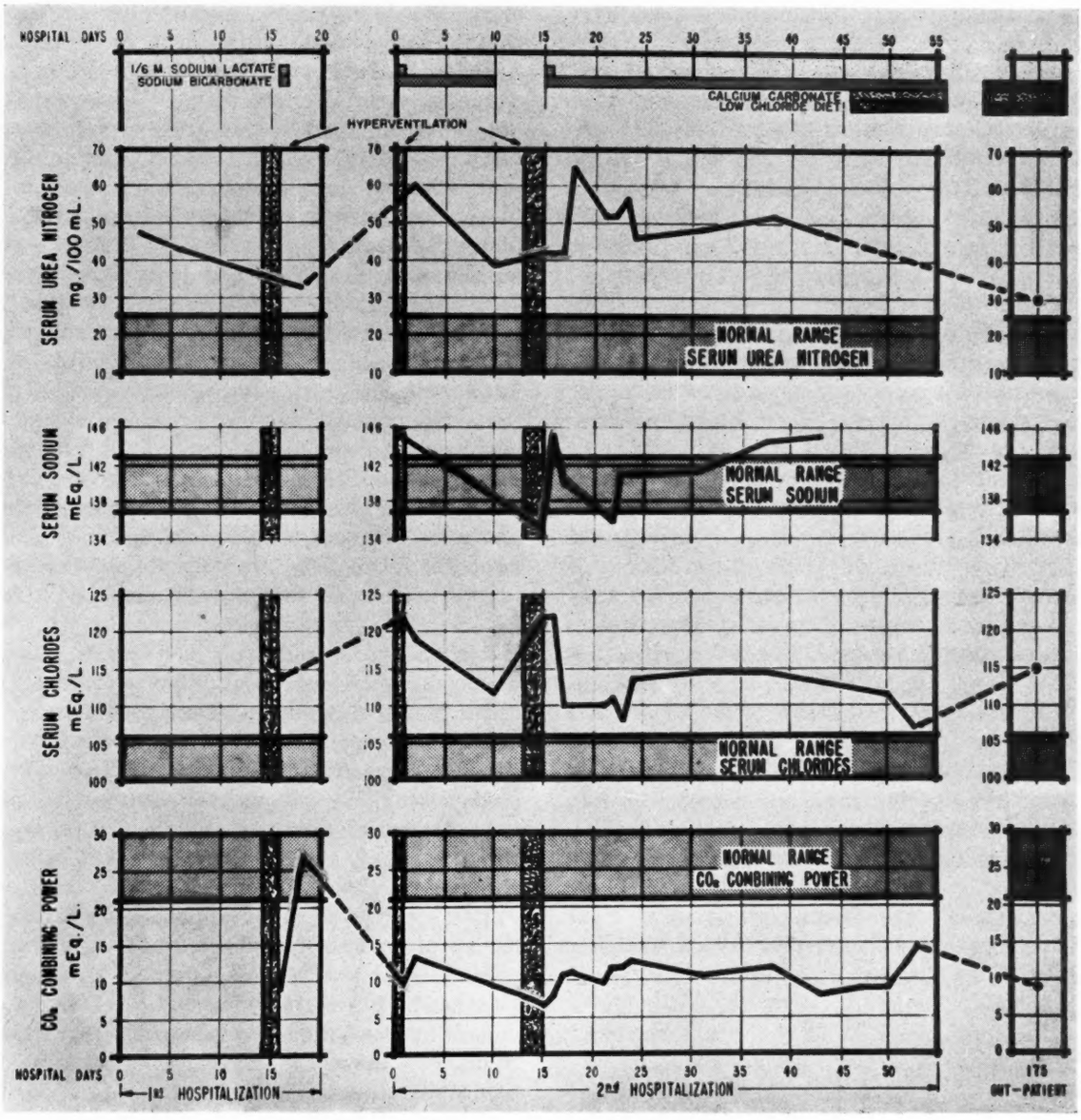

FIG. 1. Blood chemistry determinations during hospital course.

tion he remained asymptomatic except for occasional fatigue.

The finding of an elevated fasting blood glucose on the seventeenth day prompted additional studies. The fasting glucose level on the twenty-fifth day was 148 mg. per cent. An oral glucose tolerance test on the twenty-sixth day showed a fasting level of 148 mg. per cent and values of 216, 228, 191, 150 and 102 mg. per cent at thirty minutes and at one, two, three and four hours, respectively. Liver function tests, including bromsulfalein retention, serum bilirubin, thymol turbidity, and serum albumin and globulin, were all within normal limits. Blood calcium and phosphorus were likewise normal. A sternal marrow aspiration was interpreted as essentially normal and the patient's anemia was attributed to prolonged, although not severe, nitrogen retention. A reticulocyte count was 3.5 per cent. A basal metabolic rate, determined during a period when the patient was asymptomatic, was minus eleven.

On the forty-fourth day the patient was placed on a low salt diet to reduce his chloride intake and, the next day, given calcium carbonate orally in a dose of 8 gm. four times daily, in addition to his 2 gm. of sodium bicarbonate four times daily. Because this failed to produce

any significant changes in his blood chemistry, the doses were increased on the fiftieth hospital day to 12 gm. of calcium carbonate and 4 gm. of sodium bicarbonate four times daily. Two days later the carbon dioxide combining power was 32 volumes per cent (15 mEq./L.) and the serum chlorides were 107 mEq./L., representing the most nearly normal values of his hospitalization. (Fig. 1.) Further study at that time was prevented when the patient left the hospital against medical advice.

Four months later he was persuaded to return for follow-up laboratory studies on an outpatient basis. Inquiry revealed that he no longer was excessively thirsty, was having only two stools per day, felt strong, had gained weight and was working full time as an auto mechanic. He was perspiring normally and had noted no salt hunger. He had been taking his medications and diet as prescribed. A blood count showed 5,200 leukocytes with 55 per cent neutrophils, 37 per cent lymphocytes, 4 per cent monocytes, 4 per cent eosinophils and 3,810,000 erythrocytes with 11.4 gm. hemoglobin. The sedimentation rate was not increased. Blood urea nitrogen was 30 mg. per cent, carbon dioxide combining power 20 volumes per cent (9.1 mEq./L.) and serum chlorides 116 mEq./L. An oral glucose tolerance test revealed values of 110, 128, 132, 115 and 103 mg. per cent fasting and at thirty minutes, one hour, two hours and three hours, respectively. Bromsulfalein retention was 2 per cent in forty-five minutes and thymol turbidity was 2.7 units.

COMMENTS

Hyperchloremic Acidosis. Although uretero-intestinal anastomosis was first performed successfully in 1892, it was not until 1931 that Boyd[1] first called attention to acidosis as a possible sequel to the operation.

In 1950 Ferris and Odel,[2] as the result of a study of 141 patients following ureterosigmoidostomy, defined a clinical syndrome characterized by hyperchloremic acidosis and manifested by progression of easy fatigability, weakness, anorexia, nausea, vomiting, persistently salty taste with increased thirst, polydypsia, loss of weight, decrease or disappearance of the ability to perspire, decreased tolerance to cold, rectal urgency and diarrhea. Typical cases showed nitrogen retention, elevated serum chlorides and lowered plasma bicarbonate. Eighty per cent of the 141 patients studied exhibited the disturbed electrolyte pattern, but a much smaller percentage were symptomatic.

These authors presented considerable evidence upon which they based a theory of the nature of the syndrome. They noted that patients exhibiting the typical clinical picture were remarkable in showing a moderate elevation of blood urea nitrogen, despite normal blood levels of creatinine and uric acid. The kidneys were usually well visualized by intravenous pyelography and, in those cases autopsied, the kidneys appeared relatively normal. In experimental studies[3] on a large series of dogs which showed an almost identical clinical picture following ureterosigmoidostomy, the kidneys showed no evidence of infection at autopsy. In the series of Ferris and Odel[2] a return to normal blood findings was demonstrated in patients during anal incontinence, rectal lavage or the maintenance of rectal tube drainage to prevent prolonged contact of the excreted urine with the bowel wall. Transplantation of the ureters from the sigmoid colon to the skin had the same effect. These authors concluded that the changes characteristic of the syndrome are not the result of renal disease but are due to reabsorption, through the rectosigmoid mucosa, of urea and electrolytes. The electrolyte disturbance was thought to be the result of reabsorption of proportionately larger quantities of urinary chloride ion than sodium ion.

The mechanism of disproportionate chloride reabsorption is not completely understood; however, several possible explanations have been advanced. It has been suggested that the colonic mucosa might be selectively permeable to chloride ion as indicated by the experiments of Goldschmidt and Dayton.[4] Parsons et al.[5] and Annis and Alexander[6] have demonstrated experimentally that chloride is reabsorbed from the colon in excess of sodium. Various workers (Turner,[7] Parsons et al.,[5] Annis and Alexander[6]) have shown the colonic urine to be alkaline in contrast to the normally acid bladder urine. This is additional suggestive evidence of the reabsorption of acid radicles in excess of fixed base. Another possibility is that some of the urea is split by bacterial action in the bowel to form carbon dioxide and ammonia, the latter combining with chloride ion and being reabsorbed as ammonium chloride. The absorbed ammonia would then be converted by the liver to urea. Boyce[8] has demonstrated a parallel absorption of ammonia and chloride from the

colon following intracolonic instillation of ammonium chloride solution. A high activity of urea-splitting bacteria in the colon has actually been demonstrated in patients with ureterosigmoidostomy by Parsons et al.[5] These same authors suggest two other possible mechanisms, one being a chloride-bicarbonate shift in the colon, with bicarbonate replacing the absorbed chloride, and the other being sodium excretion by the bowel resulting in an apparent excess reabsorption of chloride. Foster et al.[9] point out that the ratio in milliequivalents of sodium to chloride in extracellular fluids is 1 to 0.7, in contrast to the 1 to 1 ratio in the sodium chloride molecule. Thus even the absorption of molecular sodium chloride results in a preponderance of chloride ion in the serum and, potentially, a hyperchloremic acidosis.

The increased blood concentrations of chlorides and urea lead to a compensatory diuresis which is a consistent feature of the severe acidosis associated with ureterosigmoidostomy and which may eventuate in dehydration.

Since the report of Ferris and Odel[2] a number of investigators have expressed disagreement with their views. Kekwick et al.[10] suggested that the chemical imbalance is due to renal tubular damage caused by back pressure from the colon. Lapides[11] showed that the instillation of bladder urine into the colon of patients with renal insufficiency (chronic nephritis) raised the blood levels of urea and chlorides and lowered the CO_2 combining power, but did not do so in patients with normal renal function. It should be pointed out, however, that the experimental subjects all were able to excrete urine through the normal passages, thus eliminating the factor of cyclic reabsorption through the bowel mucosa. He also stated that, in his experience, all patients with ureterosigmoidostomy and abnormal blood chemistry showed clinical evidence of recurrent attacks of pyelonephritis. He proposed that the cause of the chemical imbalance was primarily renal damage and secondarily reabsorption from the colon. He pointed out that it has been shown (Pitts and Alexander,[12] Albright et al.[13]) that hyperchloremic acidosis with a normal nonprotein nitrogen can occur in individuals with disease involving the tubular mechanism of base conservation. Pyelonephritis, the renal disease so prevalent in patients with ureterosigmoidostomy, initially involves the collecting ducts and renal tubules.

Boyce,[8] on the other hand, has reported a case with normal excretory urograms, sterile urine cultures, normal urea clearance and normal PSP excretion, but a mild hyperchloremic acidosis. The acidosis was increased during a period (post-cystoscopy) during which urea-splitting organisms could be cultured from the rectum. It could be similarly increased by a high acid ash diet or instillation of urease into the rectum. It could be corrected by catheter drainage, sterilization of the rectum with antibiotics or an alkaline ash diet. Theoretically it should be possible to differentiate the electrolyte changes occurring on the basis of reabsorption from the colon from those occurring in renal insufficiency. The colon is impermeable to sulfate[4] and almost impermeable to phosphate so that reabsorptive acidosis would be expected to be associated with normal blood levels of these anions, whereas sulfate and phosphate retention occur with even mild renal functional impairment. Ferris and Odel[2] found slight or no increase in plasma sulfate levels (0.7 to 1.3 mEq./L.) in cases of ureterosigmoidostomy exhibiting mild to moderate (24–70 mg. per cent) blood urea elevations. Additional studies are necessary to clarify this point.

It would seem likely that the urea reabsorbed from the rectosigmoid colon constitutes only a small additional load which the normal kidney promptly excretes. Cordonnier and Lage[14] state that an elevation of non-protein nitrogen is found only in cases with advanced kidney damage and that there is no relation between the non-protein nitrogen and the CO_2 combining power. Against this concept, however, is the fact that many cases exhibiting the syndrome under discussion show elevated blood urea levels but normal levels of uric acid. Also, one of the cases of Ferris and Odel[2] exhibited hyperchloremic acidosis with a normal renal capacity for chloride excretion.

In summary, the accumulated evidence indicates that some cases of hyperchloremic acidosis secondary to ureterosigmoidostomy develop solely on the basis of reabsorption from the colon of chloride and urea or ammonia. In most cases the condition is probably due to a combination of reabsorption from the colon and renal tubular damage with impaired chloride excretion.

The severity of the case here reported can be appreciated by the occurrence of most of the previously reported symptoms and by comparison of the blood chemical findings with

those of cases already recorded in the literature. Of the 141 cases reported by Ferris and Odel,[2] only nine had blood chloride levels of 120 mEq./L. or over, the highest being 131 mEq./L. Our patient showed a level of 122 mEq./L. on admission and twice after a week of treatment. One of their cases had a plasma bicarbonate of 6.1 mEq./L. None of the other cases had a level below 9 mEq./L. Our patient's lowest reading was 6.25 mEq./L. Cases with very low CO_2 combining powers have also been reported by Cordonnier[14] (5.2 mEq./L.), Parsons[5] (6 mEq./L.) and Foster[9] (6 mEq./L.). Wilkinson[15] reported a fatal case and Parsons[5] reported four fatal cases. The terminal phase in the reported fatal cases was characterized by progressive dehydration with eventual anuria. Recently, Rosenberg and Elliot[16] have reported a case, comatose on admission, with blood chlorides of 131 mEq./L. and a plasma bicarbonate of 3.6 mEq./L., but an emergency nephrostomy was required preventing long-term study.

In discussing these markedly abnormal electrolyte findings it is interesting to note that our patient nevertheless was often completely asymptomatic and able to work. In view of this fact the necessity of an attempt to restore the values to normal as a treatment measure is certainly open to question.

Hyperventilation. The most striking finding in the case reported here was the presenting complaint of very marked hyperventilation in a young man whose history showed that he had been in relatively good health only a few days previously. Its appearance in the absence of concomitant pulmonary findings, acetone or uremic odor on the breath, fever, marked nitrogen retention, or other evidence of anything but a minimal urinary infection, presented a picture which was thoroughly confusing. One of the first assumptions of the staff was that this represented a very severe case of chronic hysterical hyperventilation with compensatory chloride shift, as described by Guze et al.[17] This misinterpretation was abetted by the fact that the patient was often asymptomatic at times when the carbon dioxide combining power was as low as or only slightly higher than on admission. Furthermore, hyperventilation was not noted in the large series of cases studied by Ferris and Odel,[2] although one of their cases was as severe as ours from the point of view of blood chemistry studies. However, the case reported by Rosenberg[16] and also the case of Parsons et al.[5] had this symptom following ureterosigmoidostomy. There seems to be little doubt now that it is part of the symptom complex in sufficiently severe hyperchloremic acidosis following ureterosigmoidostomy.

In contrast to the previously reported "persistently salty taste," the symptom of salt "craving" volunteered by our patient is rather surprising. This symptom frequently accompanied polyuria when he felt ill, and at these times he consumed large quantities of salt. We can offer no explanation for this symptom.

Anemia. Anemia is not mentioned in the report of Ferris and Odel,[2] although many of their patients, of whom 82 per cent had had carcinoma of the bladder, must have exhibited this finding. Our patient's anemia, like that of uremia, did not respond well to transfusions. Although we know that a malignant process had previously existed, there were no indications of active malignant disease during the period of this study. It therefore seems quite likely that the anemia was associated with the persistent, although only moderate, blood urea elevation. If so, the substance or substances responsible for bone marrow suppression in uremia is, like the urea, capable of reabsorption through the intact bowel mucosa. The possibility that the anemia in this case was secondary to renal disease cannot be excluded, although we have no evidence that the remaining kidney was not functionally normal.

Carbohydrate Metabolism. One of the most surprising features of our case, and one not previously reported in the syndrome under discussion, is that of the disturbed carbohydrate metabolism. During the period of the patient's second hospitalization the fasting blood sugar values were repeatedly elevated and the glucose tolerance curve showed a high one-hour peak and a delayed fall. Four months later the fasting glucose level and the glucose tolerance were normal, indicating the transient nature of the disturbance. There are several possible explanations for this finding. Liver disease as a cause would appear to be excluded by the normal liver function tests. An incidental diabetes mellitus would appear highly unlikely since the disturbance in carbohydrate metabolism proved to be a transient phenomenon. During the periods of urinary tract infection and of acidosis secondary to ureterosigmoidostomy no insulin was required. The urine obtained from the rectum contained no sugar or ketones although

the carbon dioxide combining power on that day was 8 mEq./L. There was no family history of diabetes. Carbohydrate starvation must be considered a possibility, inasmuch as the patient is reported to have been "moderately undernourished" on admission and for a time suffered from anorexia and occasional vomiting. However, the regular hospital diet had been well retained for a week preceding the abnormal glucose tolerance test.

Finally, there is the possibility that carbohydrate tolerance was reduced by the acidosis *per se*. It is well known that acidosis in diabetic ketosis aggravates the disturbance in carbohydrate metabolism and may cause a marked reduction in insulin sensitivity, but only recently has it been convincingly shown that carbohydrate metabolism may be altered in acidotic states other than those due to ketosis.

In 1924 Haldane[18] reported the results of experiments done upon himself and two colleagues during which, by ingestion of large amounts of ammonium chloride, an acidosis was produced which was accompanied by elevated fasting glucose levels and decreased glucose tolerance. He suggested that ammonium chloride interferes with glycogen formation in the liver and not with the capacity for oxidation of glucose. In 1932 Gilchrist[19] compared the effects on carbohydrate metabolism of a ketogenic diet and ammonium chloride feeding. She found a moderate reduction in glucose tolerance during a ketogenic diet and only slight and inconsistent reduction in glucose tolerance during the acidosis induced by ammonium chloride ingestion. The acidosis produced was, however, milder (CO_2 combining power 40.3–49.1 volumes per cent) than that produced by Haldane and his associates who reduced the plasma bicarbonate to less than one-half of normal. These results suggest that carbohydrate metabolism is significantly altered only by relatively severe degrees of acidosis.

Guest et al.[20] have recently (1952) reported the results of a series of experiments designed to determine the effects of non-ketonemic acidosis on insulin action and on carbohydrate metabolism. They induced severe acidosis (average serum pH 7.06; average serum CO_2 content 6.3 mEq./L.) in fasting dogs by the slow intravenous infusion of M/6 ammonium chloride solution. They found a fasting hyperglycemia and impaired glucose tolerance. In severely acidotic dogs a standard dose of insulin given intravenously produced less fall in blood sugar with a slower rate of fall and a slower recovery to initial levels during the three-hour test period. Alloxan diabetic dogs showed normal insulin sensitivity until made acidotic with intravenous ammonium chloride; then sensitivity to insulin decreased. The uptake of sugar from the blood in eviscerated dogs was slower in acidotic than in non-acidotic dogs. With the influence of the liver and pancreas thus eliminated, it was concluded that acidosis inhibits the uptake of sugar by extrahepatic tissues, apart from insulin action. In acidotic blood the rate of glycolysis by the cellular elements was inhibited, more so in erythrocytes than leukocytes. These studies were considered as strongly suggestive that acidosis interferes with glycolysis by inhibiting the initial phosphorylation of glucose (probably an effect on hexokinase) rather than by affecting enzymatic reactions in the later stages of the glycolytic cycle.

Cerebral Effects. The apparent hypothermia manifested by our case may indicate another effect of acidosis on body metabolism. Unfortunately, the possible significance of this finding was not realized at the time and no series of rectal temperatures was taken to exclude the possibility of an artifact due to hyperventilation and persistent mouth breathing. Kety et al.,[21] on the other hand, have reported impairment of cerebral oxygen utilization in the presence of acidosis and it seems reasonable that acidosis *per se* may suppress the general body metabolism and heat production as well. This might also help to explain the chilly sensations and cold intolerance found in these cases. Impairment of cerebral oxygen utilization may be the cause of the drowsiness and lassitude.

Hypopotassemia. Weakness and easy fatigability are two of the commonest symptoms associated with the clinical complex under discussion and may well be related to the hypopotassemia which has been reported by several observers.[9,22] The hypopotassemia has been attributed to the increased potassium loss associated with acidosis and diuresis. The case reported by Diefenbach et al.[22] manifested complete flaccid quadriplegia and had the typical electrocardiographic findings of hypopotassemia. Both the electrocardiographic changes and the quadriplegia completely disappeared shortly after the administration of potassium chloride. An electrocardiogram was not obtained on our patient and the blood potassium levels were only slightly lowered.

SUMMARY

A case is reported showing the typical symptomatic and laboratory findings of the reabsorptive hyperchloremic acidosis following ureterosigmoidostomy. Attention is called to the additional findings of normochromic anemia and transiently disturbed carbohydrate metabolism. The possible pathogenesis of some of the abnormal findings and symptoms is discussed.

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Observations on Cold Sensitivity*

FRANK J. KELLY, M.D. *and* ROBERT A. WISE, M.D.
Houston, Texas

THIS interesting condition was first reported in 1866 by Bourdon who described a woman presenting local and systemic reactions, and by Behier who summarized his own manifestations of urticaria and syncope upon exposure to cold. In 1872 Blachez described in detail the case of a woman sensitive to cold applied to the skin or to cold fluids taken by mouth. Since the appearance of these early reports, numerous cases have appeared in the literature and have been reviewed from time to time.[1–8]

Several types of reactions to cold have been reported:

1. Localized urticaria at the point of contact, which may be anywhere on the skin and may occasionally involve the lips, tongue and pharynx if contact occurs there.

2. Localized urticaria followed by generalized urticaria.

3. Localized urticaria followed by systemic manifestations suggesting the entrance of a histamine-like substance into the circulation with resulting headache, flushing, fall in arterial blood pressure, increase in pulse rate and gastric acidity, and occasionally vertigo followed by syncope. The significance of syncope as part of a systemic response in cold-sensitive patients who go in swimming was emphasized by Horton and co-workers[5] although Behier in 1866 mentioned that he had experienced syncope after bathing in cold water.

4. Localized urticaria with hemoglobinuria. The isolated cases[2] of this combination of findings usually have syphilis as a common denominator, but not in every instance. Syphilis has not been incriminated in the cases presenting other manifestations.

5. Localized swelling associated with Raynaud's phenomenon in patients suffering from a variety of illnesses and presenting findings such as purpura, joint pain and swelling, and cryoglobulinemia. Multiple myeloma has been found more frequently than any other one disease in patients presenting this clinical picture.[9,10] Dreyfus and Librach[11] reported the presence of cryoglobulinemia without this clinical picture in 84 per cent of fifty cases of bacterial endocarditis.

6. Unusual cardiac findings have been reported in one patient by Horton[12] and another described by Duke.[13] These patients repeatedly demonstrated ventricular premature beats and altered (negative) T waves in lead III of the electrocardiogram whenever the cold stimulus was applied. Duke's case was benefited by "autodesensitization."

The role of the physical agents, heat, light and cold, in inducing or enhancing allergic responses in patients with hay fever, urticaria or asthma has been evaluated by Duke,[1] Peters and Hoffman,[14] Swineford[15] and Mathov.[16] In approximately 40 to 60 per cent of such cases the symptoms could be initiated or aggravated by physical agents particularly cold. Mathov found objective evidence (e.g., large numbers of eosinophils in the nasal mucus following immersion of the hand in cold water) in a smaller percentage of cases. This latter investigator[17] studied one hundred men who had been chronically exposed to cold, working in the freezing chambers of a meat packing plant three to six years. Some of these men were working at temperatures of −14 and −30°C.; 52 per cent experienced one or more of the following symptoms upon entering the cold rooms: rhinitis, asthma, headaches, weeping or cystalgia. Only 27 per cent presented objective findings. Urticaria was not described. The occurrence of symptoms in this group was unrelated to any personal or family history of allergy.

The general characteristics of cold-sensitive individuals have been noted by Bray[3] and by Duke[18] who emphasize that these patients, who are usually in good health, run subnormal temperatures with irregular swings; that cold is

* From the Medical Service, Veterans Administration Hospital and the Department of Medicine, Baylor University College of Medicine, Houston, Tex.

likely to produce the most marked reaction after previous exposure to internal or external heat; and that eosinophilia is rare. Study of a great number of cases reveals no consistent relationship of this form of sensitivity to the classical forms of allergy in either the patients or their families. Exceptions are the observations of Kobacker and Parkhurst[19] who reported temporary (one year) cold urticaria with eosinophilia in three sisters following measles; Kile and Rusk[20] who described one case with cold urticaria, fever and joint pains, with a family history revealing twenty-three of forty-seven relatives over five generations similarly afflicted; Urbach, Herrman and Gottlieb[7] who described one case with a history of similar symptoms in sixteen of twenty-eight members of the family over four generations; and of Witherspoon, White and Bazemore[21] who reported a young man with cold urticaria and arthralgia whose family history revealed twenty-four of forty-five members similarly afflicted. Of interest is the fact that the patients with a strong family history over several generations differ from the majority of reported cases in the following ways: symptoms begin in infancy; cold air results in generalized urticaria, joint pain and fever; pruritus is not associated with the wheals; and local application of ice or ice water does not result in a reaction. Several cases reported in the past three decades have been carefully studied. The available clinical and laboratory

TABLE I

CLINICAL AND LABORATORY FINDINGS IN FIFTY-FOUR REPORTED CASES

References—Tabulated in Chronological Order	No. Cases Studied		Localized Swelling: Lowest Temp. Required		Generalized Urticaria Following Local Stimulus	Systemic Symptoms and/or Rise in Pulse and Fall in B.P.	Increased Gastric Acidity	Eosinophilia	Passive Transfer	Reaction to Edema Fluid
	M	F								
Duke,[1] 1925	1	..	+	15°C.	0	+	−	8%—after large reaction	0	−
Horton,[12] 1927	1	1	2+	10°C.	0	+	−	−	−	−
Harris, Lewis & Vaughan,[2] 1929	2	3	4+	10–19°C.	0	+	−	−	2+	−
Horton & Brown,[22] 1929	2	2	4+	.....	0	4+	−	−	−	−
Henry,[23] 1930	..	1	+	.....	−	+	−	−	−	−
Bray,[3] 1931	1	..	+	45°F.	+	+	−	2%	−	−
Horton & Brown,[24] 1932	.. 9	..	+	8–12°C.	−	+	2+ (only ones reported)	−	−	−
Kobacker & Parkhurst[19] 1935	..	3	3+	.....	0	−	−	7, 10, 13%	−	−
Levine,[4] 1935	..	1	+	20°C.	0	+	−	1%	0	+
Saylor & Wright,[25] 1936	..	2	+	24°C. 68°F.*	−	2+	1+ (only one studied)	0	0	1+ (only case attempted)
Horton, Brown & Roth,[5] 1936	11	11	22	....	0	14	2+ (only one attempted)	−	−	−
Roth & Horton,[26] 1937	1	..	+	10°C.	0	+	+	0	−	−
Urbach, Hermann & Gottlieb,[7] 1941	1	..	0	10°F.	+†	+	−	−	−	−
Notier and Roth,[27] 1946	..	1	+	10°F.	0	+	−	−	0	−
Perry and Horton,[28] 1947	1	2	+	10°C.	0	+‡	−	−	−	−
Lerner & Watson,[9] 1947	1	..	+	....	0	+	−	−	−	−
McGovern,[29] 1948	1	..	+	48°F.	0	+	−	0	0	−
Witherspoon, White & Bazemore,[21] 1948	1	..	0	....	+	+§	−	0	−	−
Mullinger & Bogoch,[30] 1948	..	1	+	20°C.	0	+	+	0	−	−
Rothschild,[31] 1949	1	..	+	20°C.	0	+	+	7%	−	−
Sherman & Seebohm,[32] 1950	1	..	+	....	0	+	−	−	+	−
Barr, Reader & Wheeler,[10] 1950	2	..	1+	....	0	0**	−	0	−	−
Kramer & Perilstein,[33] 1951	..	1	+††		0	+	+	0	−	−
Rajka & Asboth,[34] 1951	1	3	4+	30°C.	0	1	−	2–6%	4%	−

+ = present; 0 = absent; − = not stated.

* This patient was also sensitive to heat.

† This patient sensitive to cold air (10°F.) but not to a local application of ice. Joint swelling and painful white hands and feet with numbness of fingers and toes with severe exposure.

‡ This patient also had purpura and ultimately died of chronic nephritis.

§ This patient was sensitive to cold air not to local stimulus, chills, fever and joint pains accompanied.

** Case 1 of Barr presented purpura, joint pains, urticaria, hemorrhage
Case 2 of Barr presented multiple myeloma, Raynaud's phenomenon, no urticaria

†† The local response to cold was more of a vascular spastic type than urticatial.

data are summarized in Tables I and II. Inspection of these tables reveals the following:

1. Sex distribution (as well as age distribution, not included) is random.

2. Most patients manifest a local reaction followed by systemic symptoms. Almost without exception the systemic manifestations can be prevented by applying a tourniquet proximal to the chilled part, usually the hand. Release of the tourniquet is followed immediately by systemic symptoms and signs.

3. Whenever analyzed, gastric juice increased in volume and acid content in association with the fall in blood pressure and increase in heart rate a few minutes after the local reaction.

4. The temperature required to initiate the reaction may be quite high, 30°C. being the highest reported.

5. Passive transfer tests have been successful in about one-half the instances attempted.

6. Eosinophilia is unusual.

7. Therapy by "autodesensitization," that is, repeated exposure of the affected area or the entire body, as the case may be, to progressively lower temperatures, has been effective more often than histamine "desensitization." The antihistaminic agents have been ineffective in most instances.

8. A few cases have demonstrated hemoglobinuria together with the local reaction. These patients usually have positive serologic tests for syphilis and higher titers of cold agglutinins.

9. The rare cases in whom cryogloburia has been reported differ clinically from the majority.

10. The cases sensitive to cold air but not to

TABLE II

CLINICAL AND LABORATORY FINDINGS IN FIFTY-FOUR REPORTED CASES

References—Tabulated in Chronological Order	Hemoglobinuria or Hemoglobinemia	Cold Agglutinins or Hemolysins	Cryoblobulins	Protection by Antihistaminics	Successful Autodesensitization	Successful Histamine Desensitization	Successful Histaminase Treatment	Positive S.T.S.
Duke,[1] 1925	–	–	–	–	+ Temporary)	–	–	0
Horton,[12] 1927	–	–	–	–	+	–	–	0
Harris, Lewis & Vaughan,[2] 1929	4+	4+	–	–	–	–	–	4+
Horton & Brown,[22] 1929	–	–	–	–	1+ (Only one attempted)	–	–	0 (Only 1 studied)
Henry,[23] 1930	–	–	–	–	–	–	–	–
Bray,[3] 1931	–	–	–	–	–	+	–	0
Horton & Brown,[24] 1932	1+	–	–	–	–	–	–	–
Kobacker & Parkhurst,[19] 1935	–	–	–	–	–	–	–	–
Levine,[4] 1935	0	0	–	–	Largely improved	–	–	0
Saylor & Wright,[25] 1936	0	–	–	–	–	1 Case tried with 60% improvement	–	2 0
Horton, Brown & Roth,[5] 1936	1+	–	–	–	14 Cured 5 Improved 2 Spontaneously cured 1 Not treated	–	–	–
Roth & Horton,[26] 1937	0	–	–	–	–	+	+	0
Urbach, Hermann & Gottlieb,[7] 1941	–	–	–	–	–	–	0	–
Notier & Roth,[27] 1946	–	–	–	50%	–	–	–	0
Perry & Horton,[28] 1947	–	–	–	Some temp. improvement	–	–	–	–
Lerner & Watson,[9] 1947	–	–	+	–	–	0	–	–
McGovern,[29] 1948	0	–	–	0	+ Temporary	–	–	0
Witherspoon, White & Bazemore,[21] 1948	0	–	–	Slight	–	–	–	0
Mullinger & Bogoch,[30] 1948	0	–	–	50% Transient	0	0	–	–
Rothschild,[31] 1949	0	0	–	+	+	–	–	0
Sherman & Seebohm,[32] 1950	0	0	0	0	Slight +	–	–	0
Barr, Reader & Wheeler,[10] 1950	0	0	+	–	–	–	–	0
Kramer & Perilstein,[33] 1951	0	+	–	–	–	0	–	0
Rajka & Asboth,[34] 1951	0	–	–	4+	–	–	–	0

+ = Present 0 = Absent – = Not stated

ice or cold water have a strong family history of identical reactions and symptoms usually beginning early in life.

The classic studies of Sir Thomas Lewis and co-workers over many years throw considerable light on the problem of the reactions of the skin to cold stimuli. These studies have been summarized in the Holmes Lectures for 1941[35] from which the following notes were taken. When the skin is exposed to cold its blood vessels normally contract with resultant reduced blood flow and therefore heat loss. This vasoconstriction is a composite result of three separate reactions: (1) local persistent vasoconstriction of the vessels in the chilled part, (2) transient generalized vasoconstriction on a reflex basis when any part of the body is chilled, and (3) persistent generalized vasoconstriction, presumably of central origin, resulting from the lowering of the blood temperature by mixture with the returning cooled venous blood. Local protective reactions follow when the skin is placed in contact with low temperatures (ice water). The temperature of the skin rapidly falls and, if the part exposed is small, e.g., a finger, the internal temperature likewise drops. Pain, numbness and disordered sensory and motor function result. Five to twenty minutes later local vasodilatation occurs even though the cold stimulus is maintained. This is the result of an axon reflex (it does not occur if the sensory nerves have been cut and have degenerated) and is accompanied by relief of pain, redness and increased temperature of the skin. The rise in temperature may amount to several degrees even if the skin is immersed in ice water and, if removed, the temperature rises well above that of the unexposed skin. The vasodilatation described is seen with many forms of injury to the skin and suggests local release of a histamine-like substance. With rapid cooling to low temperatures (−5 to −10°C.) wheal and flare may appear in an occasional subject. If the skin is rapidly taken to still lower temperatures (−10 to −15°C.) for twenty seconds, a wheal and flare usually follow. If the temperature is maintained at −15°C. for thirty to sixty seconds or at −20°C. for fifteen to thirty seconds, the wheal appears and, in an hour or so, is followed by a blister. With prolonged cooling (two hours at 5°C.) the exposed part is red and swollen, as much as 15 per cent increase in volume has been observed. Patients who have experienced cold injury in one portion of the body are likely to show earlier or exaggerated responses in this part on subsequent exposure.

The changes in blood pressure and pulse rate during the first five minutes after immersion of one hand in ice water have been studied extensively as the cold pressor test designed to detect individuals with hyperactive sympathetic nervous sytems.[36,37] The normal individual displays a slight rise in systolic and diastolic pressure whereas the changes in pulse rate are not notable. Approximately 15 per cent of normal individuals and three to four times as many hypertensive patients react with larger increases in systolic and diastolic pressure and little change in pulse rate. Following thoracolumbar sympathectomy there is a slight reduction in the percentage of patients hyperacting to the cold pressor test according to Smithwick.[38]

Thus the sequence of local reactions described by Sir Thomas Lewis in normal individuals whose skin has been briefly exposed to very low temperatures (−10 to −20°C.) or to somewhat higher temperatures for a prolonged period (up to two hours) is observed in the cold-sensitive patient at a considerably higher temperature (reactions at 30°C. have been described) and after a very brief exposure. In some patients the usual response of the blood pressure and pulse rate to such a stimulus is overbalanced because of the effects of a humoral substance released from the injured areas. This substance is similar to histamine. In our opinion the available evidence suggests that such patients differ only quantitatively from normal subjects in the reactivity of their tissues to a commonly experienced stimulus. Such altered reactivity of the tissues may appear spontaneously or may possibly be induced by injury of a different type, as is suggested in the case reported. This opinion is in essential agreement with that expressed by Horton et al.[5,22,24] and Bray[3] many years ago. It differs from that held by Duke[1,18] who believed that the patients displaying systemic reactions had a defect in the heat-regulating mechanism of the body whereas those presenting localized reactions were considered to be similar to patients with localized drug allergies. The more elaborate classification of various types of physical allergy proposed by Urbach, Herrman and Gottlieb[7] seems unnecessary and confusing.

It is interesting to speculate that the reaction displayed by this type of patient is the antithesis of Raynaud's phenomenon. It may well be that the latter type of patient lacks those local

factors, the release of which upon cold stimulation gives rise to protective vasodilatation. The lack of local protective factors as the responsible agent in Raynaud s disease may explain the failure of sympathectomy to cure the condition. Harris, Lewis and Vaughan discuss this problem and describe, from the literature, cases presenting Raynaud's phenomenon, localized swelling and urticaria. Some of these cases demonstrated gangrene of the skin. All were males. The last two observations are rare in patients presenting Raynaud's disease in its usual form. With the exception of these cases and those demonstrating cryoglobulinemia, Raynaud's phenomenon is not a part of the usual picture of cold sensitivity.

CASE REPORT

E. B. (Hosp. No. 17056), a twenty-nine year-old single white male oil refinery worker, was admitted to the psychiatric service of the Veterans Administration Hospital, Houston, Texas, January 31, 1952, with symptoms leading to the diagnosis of chronic, severe schizophrenic reaction of the paranoid type. On April 10, 1952, he was transferred to the Medical Service for investigation of swelling of the hands on exposure to low temperatures. This complaint was not one of his presenting symptoms.

At this time the following history was obtained: In 1943, shortly after entering the army he was stationed in Florida for jungle warfare training. Here he acquired a skin disease of the hands characterized by rash followed by desquamation. He was hospitalized fifteen days for this problem and was given no definite diagnosis. Following discharge the skin of the hands gradually returned to normal over a period of several weeks. Subsequently, he was sent to England and Ireland and there drove a truck. At this time he first noted that his hands would swell slightly when exposed to low temperature, especially if he would take hold of the steering wheel of his truck on a cold morning. Ever since then, and with gradual increase in severity, he has noticed that his hands swell when cold.

This has been true since his discharge from the army in 1945, even though he has lived in Galveston, Texas, where the winters are quite mild. If he failed to wear gloves on leaving his home in the morning during winter his hands would become so swollen after holding the steering wheel of his automobile while driving to work that he could not properly adjust the valves and gauges in the oil refinery in which he works. During the summer, holding a cold glass or bottle resulted in swelling of the hand involved. Within five to ten minutes of exposure the hands began to feel stiff, got red, and began to tingle. Pain might appear if the swelling were particularly severe. He had to remove his ring before the reaction set in because it would become tight. The fingers and hands up to the wrist swelled equally and he could flex the fingers only slightly. Maximum swelling occurred in ten to fifteen minutes and gradually subsided over a few hours. Immersion in warm water aggravated the situation rather than stopping or relieving it. No other part of his body swelled when cold or when the hands became swollen. If the hands were protected, exposure of other parts of the body to low temperatures did not result in swelling of the hands. No other stimulus resulted in this reaction. There have been no systemic symptoms accompanying the changes in the hands. Recovery was complete in a few hours and no changes in the skin have been noted even after repeated occurrences of swelling within a few days.

The past medical history and systemic review were otherwise non-contributory. He never had hay fever, hives, asthma or drug reactions, nor was there a family history of allergy or of a similar sensitivity to low temperature.

Physical examination on admission to the psychiatric service and while on the Medical Service was well within normal limits. His arterial blood pressure was 140/100 mm. Hg on admission and fell to the range of 140/70 to 80 mm. Hg with daily observation. The hands appeared normal. Temperature, pulse and respiration remained normal during hospitalization.

Laboratory data and accessory clinical findings were as follows: Red blood count 5.85 million, hemoglobin 16.8 gm., hematocrit 47 per cent, white blood count 8,200, differential: polymorphonuclears 53 per cent, stab forms 1 per cent, lymphocytes 40 per cent, eosinophils 3 per cent. Urinalysis: clear, pH 5.5, specific gravity 1.027, albumin and sugar negative, microscopic examination showed some oxalate crystals. Cold agglutinins were not demonstrated. Mazzini and Kahn tests were negative. Roentgenographic examination of the chest, skull, spine and gastrointestinal tract was normal. Lumbar puncture revealed normal pressure, clear fluid containing 4 lymphocytes, 35 mg. per cent protein, flat colloidal gold curve, and negative Kolmer test. Basal metabolic rate was

minus 11 per cent; maximum uptake of radioactive iodine by the thyroid gland was 14.2 per cent at forty-eight hours, which is within normal limits for the method used. Glucose tolerance test (three hours) was normal. Electroencephalogram, visual field examination and neurologic consultation revealed no abnormalities. Ear, nose and throat evaluation likewise revealed no disease. The electrocardiogram was normal.

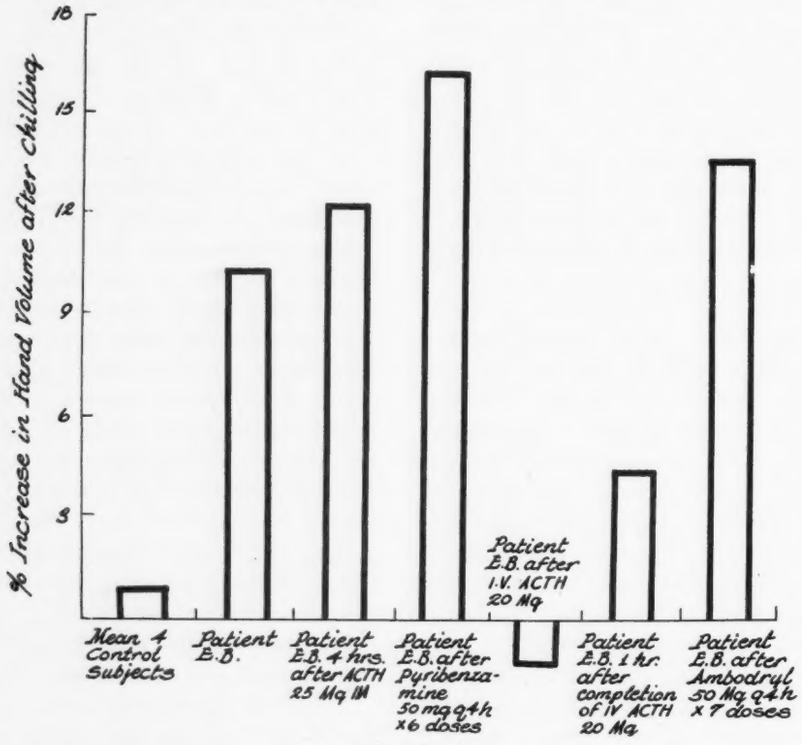

FIG. 1.

In order to evaluate the degree of swelling of the hands quantitatively so that the reaction could be studied under various circumstances a simple method of measuring the volume of the hands by displacement was used. A line was drawn about each wrist with a skin-marking pencil and the hand inserted into a large beaker of water (temperature 35°C.). When the fluid had come to rest, the level of the meniscus was marked on the outside of the beaker. The hand was withdrawn and allowed to drain. The fluid level was then restored to the previous mark. The volume required to return to the original mark represented the volume of the hand. This technic was easily carried out in a minute and repeated determinations gave surprisingly good agreement (1 to 2 per cent). In all studies the volume of each hand was measured and one hand immersed for two to three minutes in ice water (temperature 2 to 4°C.). Subsequent measurements of each hand were made between ten to twenty minutes after exposure to cold. Four members of the laboratory staff were studied as controls. Results of these studies are presented graphically, in the order carried out, in Figure 1. The mean change in the volume of the chilled hand of the four control subjects was plus 1 per cent, two subjects showing a slight decrease and two a slight increase in volume. The unchilled hand of the controls likewise demonstrated an insignificant change in volume. Following immersion of one of the patient's hands in ice water the volume increased 10 to 16 per cent. The unchilled hand did not change significantly.

The administration of two antihistaminic agents (pyribenzamine and ambodryl) in large therapeutic dose—50 mg. every four hours for twenty-four and twenty-eight hours, respectively—prior to testing on two different occasions failed to inhibit the response. Four hours after the intramuscular injection of 25 mg. of ACTH, which resulted in a fall in circulating eosinophil count from 55 to 35 cells per cu. mm., the reaction was unchanged. However, when 20 mg. of ACTH were given by continuous intravenous drip over a six-hour period followed immedi-

ately by testing, the swelling failed to occur. Thirty to sixty minutes later a second chilling of the same hand resulted in a 4.9 per cent increase in volume.

On one occasion the possibility of circulating factors was investigated in the following manner. With the patient in the postabsorptive state and at bed rest for one hour, the blood pressure and pulse rate were noted and blood was withdrawn without tourniquet from each antecubital vein. One hand was then chilled in the usual fashion and swelling of the expected magnitude occurred. At the time swelling was maximal the pulse rate and blood pressure were again determined and blood withdrawn from each antecubital vein. There was a slight increase in pulse rate (12 per minute) and a slight fall in blood pressure (15 mm. Hg systolic and 9 mm. Hg diastolic). The blood withdrawn from the antecubital vein on the side of the chilled hand was almost as red as arterial blood, whereas that removed from the side of the unchilled hand was definitely venous in color. The eosinophil count fell from 50 per cu. mm. to 35 per cu. mm. (30 per cent) in the blood from the side of the chilled hand and did not change in blood from the control side. There was no significant change in total white blood cell count or differential white blood cell count in blood from either arm. Circulating hemoglobin, cryoglobulins or Coomb's antibodies were not demonstrated in blood from either arm before or after chilling.

Two control subjects were studied in a similar although less complete manner. Blood was withdrawn from each antecubital vein before and after one hand was chilled. No change from the usual venous color occurred. One subject demonstrated a fall in eosinophil count in blood withdrawn from the side of the chilled hand, from 313 to 310 cells per cu. mm. (1 per cent) while the count of the blood from the unchilled side fell from 365 to 332 cells per cu. mm. (9 per cent). In the other control subject the eosinophil count increased 8.3 per cent (108 to 117 cells per cu. mm.) on the chilled side and fell 23 per cent (112 to 86 cells per cu. mm.) on the warm side. No significant change in pulse rate or blood pressure was observed.

Immersion of the patient's foot in ice water was not followed by swelling of either the foot or of the hands. Application of a piece of ice to the skin of the forearm did not result in a local reaction nor did either hand change.

Several weeks after the first of many applications of cold stimuli the reaction began to decrease in severity. Neither hand would swell to a significant degree. This is of interest since only one hand (the right) was usually chilled in the course of study.

It would seem logical to conclude that the swelling limited to the hands of the patient represents a localized alteration in the reactivity of the tissues probably related to the skin disease of the hands which preceded the onset of this phenomenon. Whether the primary defect is in the reactivity and permeability of the arterioles, capillaries and venules, or whether the tissues liberate a histamine-like substance on exposure to low environmental temperature cannot be decided from these studies. The arterialization of the venous blood returning from the swollen hand, the slight increase in pulse rate and fall in arterial blood pressure are compatible with the action of a histamine-like substance. Hemagglutinin, cold precipitable globulin or hemoglobinemia was not found. The fall in eosinophil count in the blood taken from the vein draining the swollen hand and its absence from the blood taken from the opposite arm are interesting observations in view of the reports of Bray[3] and of Levine[4] in which the eosinophil count of capillary blood taken from the swollen fingertips of their patients showed a slight increase in the percentage of eosinophils (2 per cent to 4 per cent and 1 per cent to 6 per cent before and after chilling) seen in the differential blood count. Perhaps there is some degree of collection of eosinophils in the edema fluid or capillaries under these circumstances. Support for this is presented in the histologic studies of wheals produced in allergic individuals by skin testing and in allergic and non-allergic individuals by injecting histamine.[39] In these studies tissue eosinophilia developed fifteen minutes after the appearance of the wheal. After thirty minutes the eosinophils predominated. The eosinophil response was more marked in allergic subjects.

SUMMARY

A case demonstrating unusual sensitivity of the hands to exposure to low environmental temperatures, with resultant swelling, is presented, together with quantitative observations on the influence of various drugs. It is concluded that the case is an example of acquired altered reactivity of the vasculature of the hands,

possibly associated with liberation of histamine-like substances in the tissues. This condition is thought to be secondary to an undiagnosed skin disease of the hands which preceded the onset of the reaction by a few months. Two antihistaminic agents and intramuscular ACTH failed to alter the response. Intravenous ACTH blocked the reaction temporarily.

The literature of the past three decades has been reviewed and evaluated.

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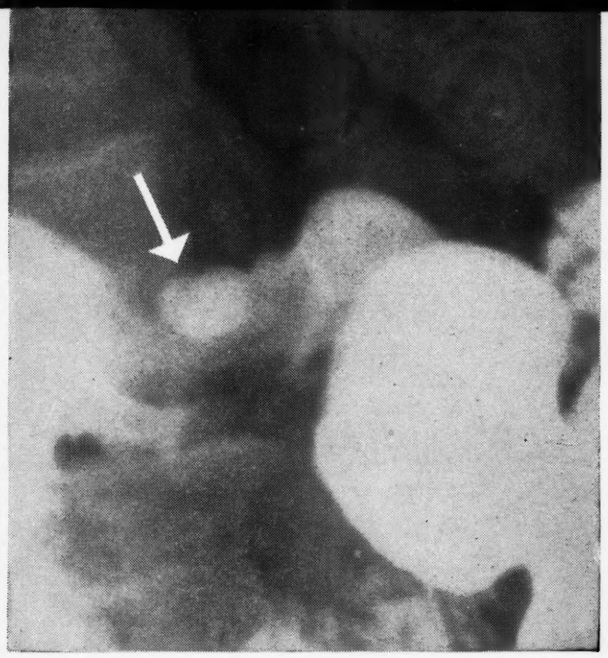
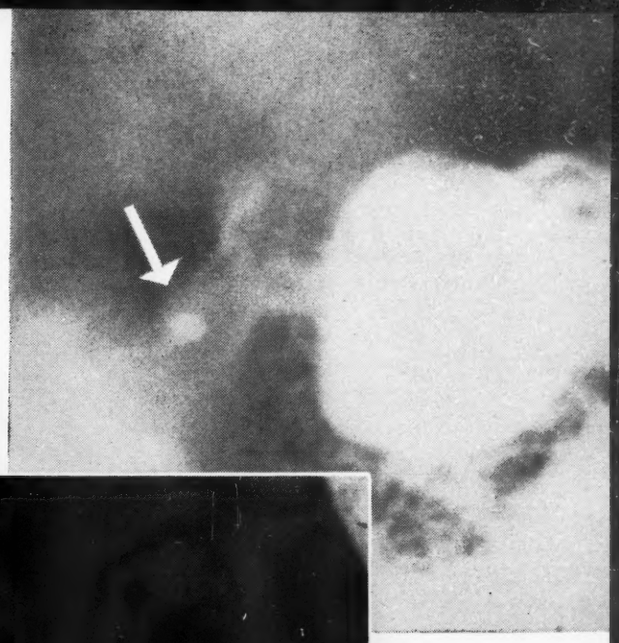
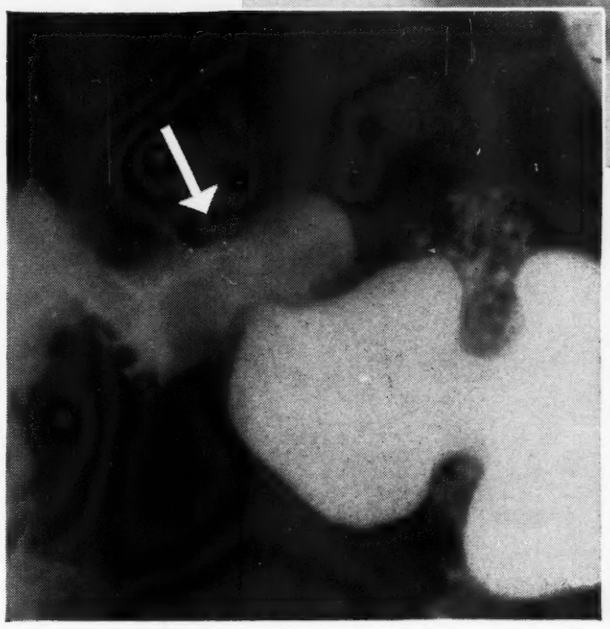






Top left: "X-rays revealed a huge ulcer crater in the duodenal bulb."

Top right: "Twelve days later the crater was strikingly reduced in size."

Bottom: "Two weeks later another spot roentgenogram revealed complete healing."

Rapid Healing of Duodenal Ulcer with Pro-Banthine®

CASE REPORT

J. L., male, age 39, refused surgery even though roentgen study revealed a huge ulcer crater in the duodenal bulb (top left). He was placed on a Pro-Banthine regimen of 30 mg. four times a day. After twelve days of therapy the crater was strikingly reduced in size (top right).

Two weeks later another spot roentgenogram revealed complete healing (bottom). "This ulcer crater was unusually large, yet on 30 mg. of Pro-Banthine [q.i.d.] the patient's symptoms were relieved in forty-eight hours and a most dramatic diminution in the size of the crater was evident within twelve days."

Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

Pro-Banthine (brand of propantheline bromide) is a new and improved anticholinergic agent with minimal or no side reactions.

Pro-Banthine inhibits neural impulses at both the sympathetic and parasympathetic ganglia and at the postganglionic nerve endings of the parasympathetic system. It is valuable in many conditions in addition to peptic ulcer, notably gastritis, pancreatitis, intestinal hypermotility, genitourinary spasm and hyperhidrosis.

Pro-Banthine is available in three dosage forms: 15 mg. sugar-coated tablets; Pro-Banthine (15 mg.) with Phenobarbital (15 mg.), sugar-coated tablets, for use when anxiety and tension are complicating factors; ampuls of 30 mg. for more rapid effect and in instances when oral medication is impractical or impossible.

SEARLE *Research in the Service of Medicine*

Do you have all the facts on these

Important Anticonvulsants

TRIDIONE®

(Trimethadione, Abbott)

First successful synthetic agent—now agent of choice—for the symptomatic control of *petit mal*, myoclonic jerks and akinetic seizures.

PARADIONE®

(Paramethadione, Abbott)

Homologue to TRIDIONE. An alternate preparation which is often effective in cases refractory to TRIDIONE therapy. For treatment of the *petit mal* triad.

GEMONIL®

(Metharbital, Abbott)

A new drug of low toxicity for *grand mal*, *petit mal*, myoclonic and mixed seizures. Effective in conditions symptomatic of organic brain damage.

PHENURONE®

(Phenacemide, Abbott)

A potent anticonvulsant for psychomotor epilepsy, *grand mal*, *petit mal*, and mixed seizures. Often successful where all other forms of therapy have failed.

These are names to remember. Each, in turn, has signaled a dramatic advance in the field of anti-epileptic medicine. Used properly, discreetly, these four drugs will add inestimably to the scope and progress of your treatment of various epileptic disorders. Write us today for literature on any or all of these important anticonvulsants. Abbott Laboratories, North Chicago, Illinois.

Abbott

1-165

an agent of choice in urinary tract infections

- *promptly effective against a broad-spectrum of urinary pathogens*
- *high concentration in active form in urinary tract*
- *well tolerated, even upon prolonged administration*

Terramycin is acclaimed by urologists everywhere for unsurpassed action in

chronic urinary tract infections

acute urinary tract infections

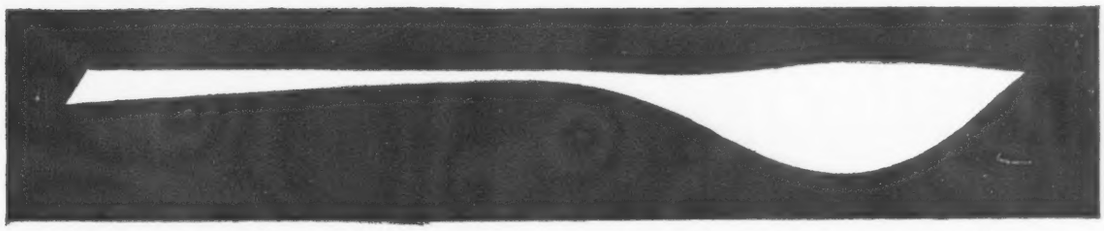
urinary tract surgery

Pfizer PFIZER LABORATORIES.

To accelerate recovery in the common anemias

"Bemotinic" *liquid and capsules*

These two dosage forms provide essential factors — including a B_{12} potentiator — for maximal hemopoietic and clinical response.

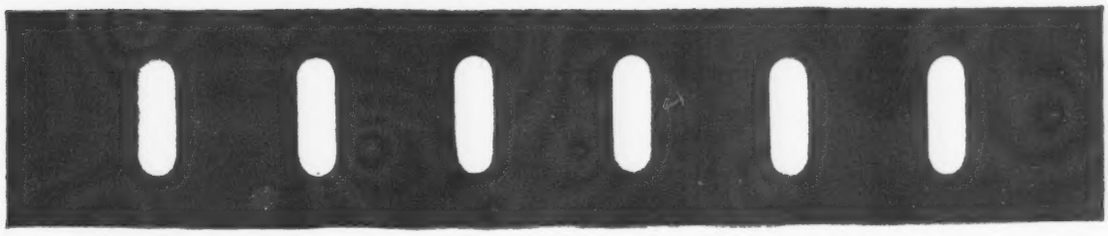


"Bemotinic" Liquid — Unequalled for taste — pleasantly rich orange-flavor with no aftertaste — no need to dilute or mask — smooth, nonviscous, easy pouring — nonalcoholic.

Each teaspoonful (5 cc.) contains:

Ferric ammonium citrate	200.0 mg.	Folic acid	0.33 mg.
Vitamin B_{12} U.S.P. (crystalline)	4.0 mcg.	Thiamine HCl (B_1)	1.5 mg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.	Riboflavin (B_2)	1.0 mg.
		Pyridoxine HCl (B_6)	0.2 mg.

Suggested Dosage: Adults: 1 to 2 teaspoonfuls. Children: ½ to 1 teaspoonful. Three times daily, or more as required. Preferably taken with food.
No. 940 — Supplied in bottles of 16 fluidounces and 1 gallon.



"Bemotinic" Capsules

Each capsule contains:		Desiccated liver substance, N.F.	100.0 mg.
Ferrous sulfate exsic. (3 gr.)	200.0 mg.	Folic acid	0.67 mg.
Vitamin B_{12} U.S.P. (crystalline)	10.0 mcg.	Thiamine HCl (B_1)	10.0 mg.
Gastric mucosa (dried)	100.0 mg.	Vitamin C (ascorbic acid)	50.0 mg.

Suggested Dosage: 1 or 2 capsules three times daily, or as directed by the physician. Preferably taken with food. No. 340 — Bottles of 100 and 1,000.

Ayerst®

Ayerst, McKenna & Harrison Limited • New York, N. Y. • Montreal, Canada

5303

introducing

Cortef*

for topical anti-inflammatory therapy of dermatitis

A completely new approach to the management of dermatitis has been achieved. Upjohn scientists have developed Cortef Acetate Ointment for the application of the most active adrenal steroid —compound F—into affected skin layers.

Up to now, the conventional treatment of dermatitis has been primarily empirical and symptomatic (e.g., calamine for pruritus). Cortef Acetate Ointment offers a new approach through its anti-inflammatory effect. It permits the full utilization of the anti-inflammatory activity of compound F (hydrocortisone) at the tissue level without producing systemic effects.

Unlike cortisone, compound F (hydrocortisone) is effective on the skin. Results are often immediate and striking: lesions turn pale and flat; erythema, edema, and infiltration subside. And in the many instances where atopic dermatitis is self-limited, quick suppression of symptoms with Cortef Acetate Ointment may prove tantamount to cure.

Even cases refractory for years or decades to other forms of treatment have been reported yielding to the new hormonal therapy with Cortef Acetate Ointment.

acetate ointment Upjohn

(BRAND OF HYDROCORTISONE ACETATE)

SUPPLIED:

Cortef Acetate Ointment is available in 5 Gm. tubes in two strengths—2.5% concentration (25 mg. per Gm.) for initial therapy in more serious cases of dermatitis, and 1.0% concentration (10 mg. per Gm.) for milder cases and for maintenance therapy.

ADMINISTERED:

A small amount is rubbed gently into the involved area one to three times a day until definite evidence of improvement is observed. The frequency of application may then be reduced to once a day or less, depending upon the results obtained.

* *Trademark*

A product of Upjohn Research *for medicine . . . produced with care . . . designed for health*

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Announcement

an advance in therapy of adrenocortical insufficiency

Percorten® trimethylacetate

DESOXYCORTICOSTERONE TRIMETHYLACETATE CIBA

Intramuscular repository

"A month's therapy with a single injection." Therapy of chronic adrenocortical insufficiency has been improved and made more convenient to both patient and physician by Ciba's introduction of Percorten trimethylacetate in the form of a long-acting microcrystalline suspension.[1-5] • A single injection of this new long-acting steroid hormone derivative provides maintenance therapy for about a month. • This protracted and constant therapeutic effect is achieved because the suspension, when administered by deep intramuscular injection, simulates a miniature pellet in that a small fraction of the total dose is absorbed daily. • Patients who have Addison's disease and who are not in crisis can now be treated on a highly satisfactory ambulatory basis.

Indications: Chronic primary and secondary adrenocortical insufficiency, and hypotension associated with adrenal insufficiency. **Supplied:** Multiple-dose vials—4 ml. containing 25 mg./ml. as an aqueous suspension for intramuscular use only. **Note:** Percorten (desoxycorticosterone Ciba) is available in 4 administration forms: (1) Percorten trimethylacetate, long-acting intramuscular repository, aqueous suspension; (2) Percorten acetate in oil solution, for intramuscular injection; (3) Percorten acetate Linguets,® for sublingual or parabuccal absorption; (4) Percorten acetate pellets, for subcutaneous implantation.

Ask your Ciba professional service representative or write the Medical Service Division for complete information on the use of Percorten trimethylacetate.

1. Gross, F., and Tschopp, E.: Experientia *8*:75, 1952. **2.** Thorn, G. W., and Jenkins, D.: In press. **3.** Thorn, G. W.; Jenkins, D.; Arons, W. L., and Frawley, T. F.: Schweiz. med. Wchnschr. *82*:697, 1952. **4.** Gaunt, R.; Leathem, J.; Howell, C., and Antonchak, N.: Endocrinology *50*:521, 1952. **5.** Sorkin, S. Z., and Soffer, L. J.: Am. Fed. Clin. Research, May 4, 1952.

Ciba *Summit, New Jersey*

2/1918M

You can't insulate your patient

against the stresses of modern life . . .

You can help him secure tranquillity by prescribing a judicious combination of low-dosage sedation and therapeutic vitamin intake...including substantial quantities of Vitamin B_{12}.

BEPLETE®

VITAMINS B COMPLEX WITH PHENOBARBITAL

Elixir Tablets

Wyeth®

Philadelphia 2, Pa.

Announcing

A NEW DRUG... for control of blood pressure

UNITENSEN

Brand of Cryptenamine (Irwin-Neisler) TRADE-MARK

Unique Advantages of **UNITENSEN**

- Of all the known Veratrum alkaloids or Veratrum alkaloid preparations, Unitensen, brand of cryptenamine, is the only one which has a 4:1 ratio between its hypotensive activity and the dosage level which produces the side effect of vomiting.
- Unitensen assures a wide margin between therapeutic and vomiting dose by means of a dual biologic standardization for both emetic propensities and hypotensive action.
- Unitensen has a therapeutic index of 125—highest of all available Veratrum alkaloids tested.
- Unitensen has consistent, predictable and uniform action.

COMPARISON OF UNITENSEN WITH PROTOVERATRINE AND THREE OTHER ALKALOID PREPARATIONS

Drug	Emetic: Therapeutic Ratio	Therapeutic Index
UNITENSEN (cryptenamine—Irwin, Neisler)	4:1	125
Protoveratrine A & B	1:1	20
Commercial Alkaloid Preparation A	1.2:1	40
Commercial Alkaloid Preparation B	1:1	—
Commercial Alkaloid Preparation C	1:1	—

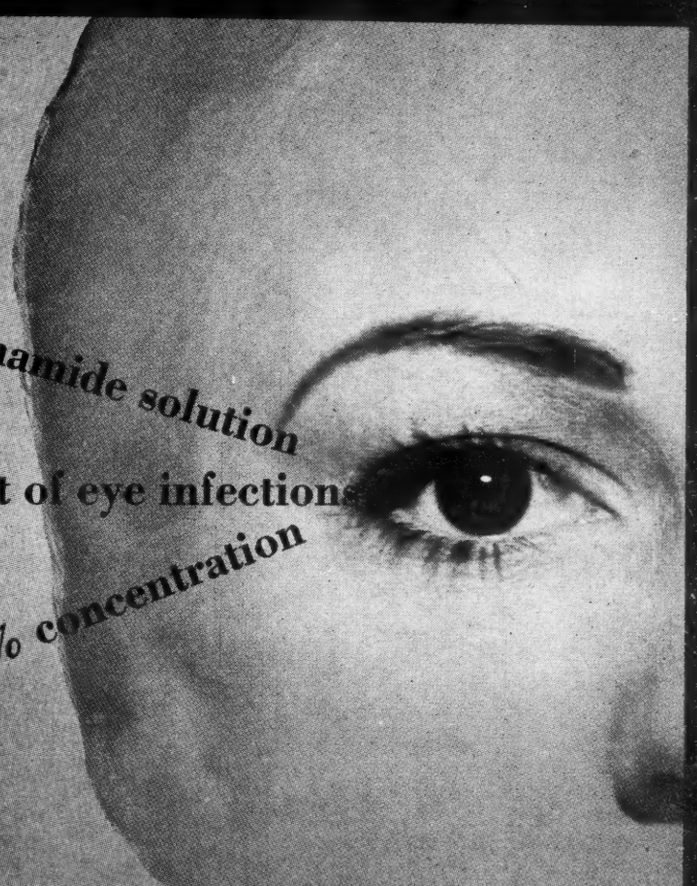
Unitensen has shown excellent results in clinical studies in hypertensive crisis, eclampsia, preeclampsia, and preeclampsia with underlying essential hypertension.

Unitensen (Aqueous) is available at present as a parenteral preparation, containing 2 mg. per cc. (260 C.S.R.* Units) of cryptenamine, in 5 cc. multiple dose vials.

*Carotid Sinus Reflex

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

Research to Serve Your Practice



sulfonamide solution

for prevention and treatment of eye infections

in 30% concentration

Higher concentration—Sodium SULAMYD® Ophthalmic Solution provides sulfacetamide, a sulfonamide soluble to a concentration of 30% *at physiologic pH*.

Wide therapeutic range—Effective against all common eye pathogens, both gram-positive and gram-negative.

Rapid, deep penetration—Higher solubility and concentration produce local therapeutic levels within 15 minutes.

Excellent results—In eye injury—no loss of working time in 98.87 per cent of one series of 11,953 cases; in eye infections—rapid healing.

Well tolerated—Outstanding freedom from irritation and sensitization.

Sodium SULAMYD Ophthalmic Solution 30%

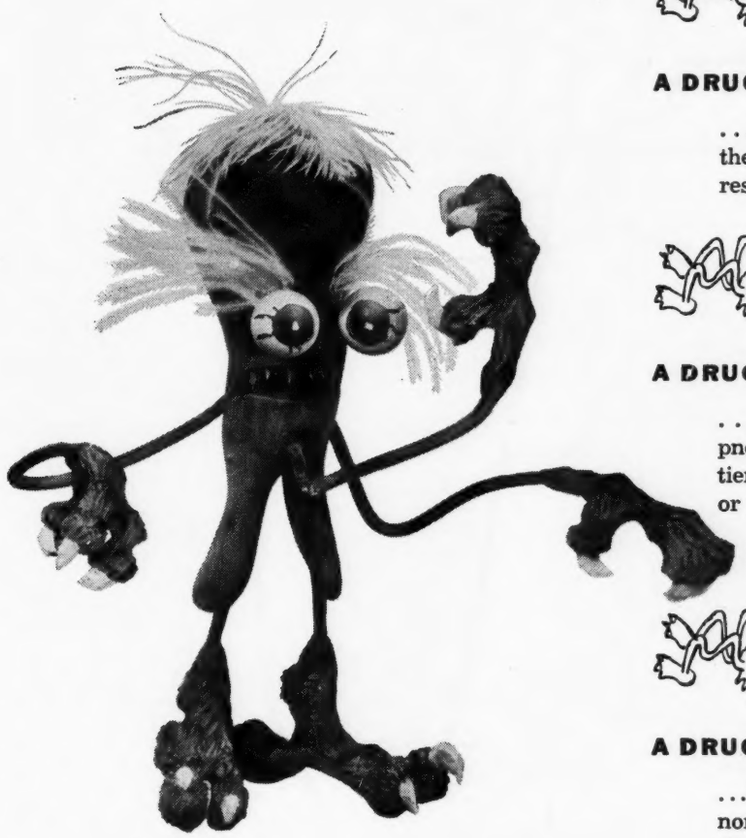
(Sodium Sulfacetamide–Schering)

Sodium SULAMYD Ophthalmic Solution 30%: 15 cc. eye-dropper bottles.

Sodium SULAMYD Ophthalmic Ointment 10%: ⅛ oz. tubes.

Schering CORPORATION • BLOOMFIELD, NEW JERSEY

Sodium SULAMYD Ophthalmic Solution 30%



When is ERYTHROCIN* an antibiotic of choice?

A DRUG OF CHOICE

. . . against staphylococci—because of the high incidence of staphylococcic resistance to other antibiotics.

A DRUG OF CHOICE

. . . orally against streptococcal and pneumococcal infections, when patients are sensitive to other antibiotics or these cocci are resistant.

A DRUG OF CHOICE

. . . because it does not materially alter normal intestinal flora; gastrointestinal disturbances are rare; no serious side effects reported.

ADVANTAGEOUS

. . . because the special acid-resistant coating, developed by Abbott, and Abbott's built-in disintegrator, assure rapid dispersal and absorption in the upper intestinal tract.

USE ERYTHROCIN

. . . in pharyngitis, tonsillitis, scarlet fever, pneumonia, erysipelas, osteomyelitis, pyoderma and other indicated conditions. Abbott

* *Trade Mark for*
ERYTHROMYCIN, ABBOTT, *CRYSTALLINE*

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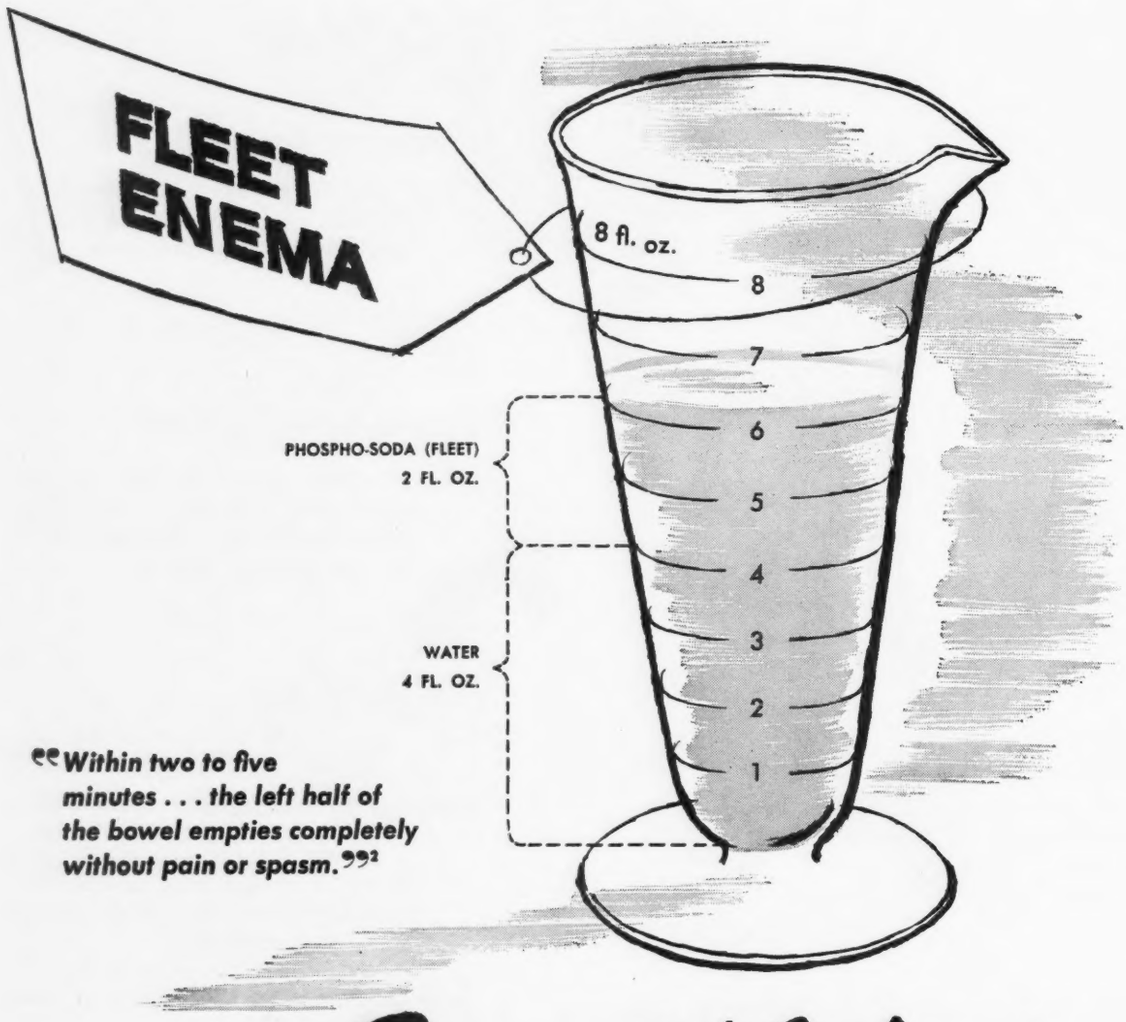

"Within two to five minutes . . . the left half of the bowel empties completely without pain or spasm."[2]

Segmental Catharsis

. . . with the Fleet Enema — safe, simple, time-saving

. . . **preferred** over other enema preparations because of its "distinct advantage in safety and effectiveness,"[2] particularly when purging of the entire gastrointestinal tract is not required.

. . . **clinically proved**[1,2,3,4] by more than four years of extensive use—for preoperative cleansing and general postoperative use — in preparation for proctoscopy and sigmoidoscopy — to relieve fecal or barium impactions — for use in collecting stool specimens — and as a routine enema.

The only stable aqueous solution of the two U. S. P. sodium phosphates—containing in each 100 cc. sodium biphosphate 48 Gm. and sodium phosphate 18 Gm.

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NOTABLY SAFE AND EFFECTIVE WHENEVER LAXATION IS INDICATED

1. Burnikel, R. H. and Sprecher, H. C.: Am. J. Dig. Dis. 19:191, 1952.
2. Marks, M. M.: Am. J. Dig. Dis. 18:219, 1951; personal communication, 1952.
3. Sweatman, C. A.: J. South Carolina M. A. 49:38, 1953.
4. Hamilton, H.: Trans. 5th Am. Cong. Obst. & Gyn., Mosby, 1952, p. 69.

C. B. FLEET CO., INC., LYNCHBURG, VA.

there is only one **PHOSPHO-SODA** *(Fleet)*®

THESODATE

THE ORIGINAL ENTERIC-COATED TABLET OF THEOBROMINE SODIUM ACETATE

provides

EFFECTIVE
WELL-TOLERATED
PROLONGED
VASO-DILATION

REPEATEDLY SHOWN and proven by objective tests on human subjects[1] — this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus THESODATE, with its reasonable prescription price also, enjoys a greater patient acceptability.

in

CORONARY ARTERY DISEASE

Available: **In bottles of 100, 500, 1000.**

TABLETS THESODATE

***(7½ gr.) 0.5 Gm. *(3¾ gr.) 0.25 Gm.**

THESODATE WITH PHENOBARBITAL

***(7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.**
(7½ gr.) 0.5 Gm. with (¼ gr.) 15 mg.
***(3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.**

THESODATE WITH POTASSIUM IODIDE

(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

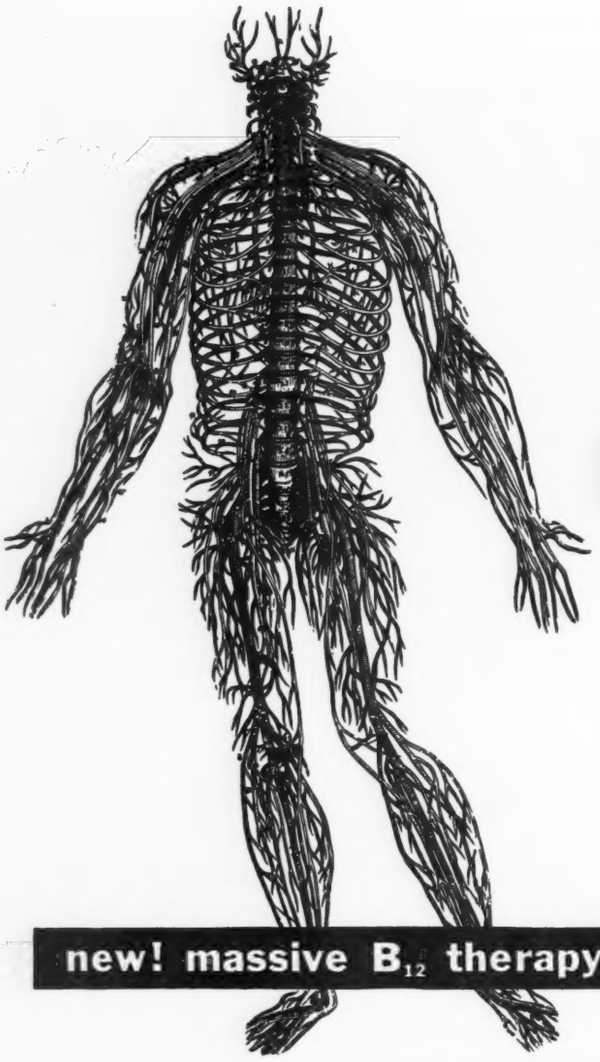
***In capsule form also, bottles of 25 and 100.**

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

For samples just send your Rx blank marked — 13TH9

Brewer EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.



dramatic,
sustained relief
in
severe

nerve pain

of

trigeminal neuritis
diabetic neuritis
subacute combined sclerosis (of pernicious anemia)
peripheral neuritis
herpes zoster
tabes dorsalis

new! massive B_{12} therapy...

DODECAVITE

1000 mcg. vitamin B_{12} per cc.

for intramuscular or subcutaneous injection

Complete or long-time remission of pain in a substantial number of patients • often successful where all other therapy has failed • non-toxic • well worth trying in these disabling, agonizing pain conditions which so often leave the physician so helpless and the patient so hopeless.

Detailed literature upon request.

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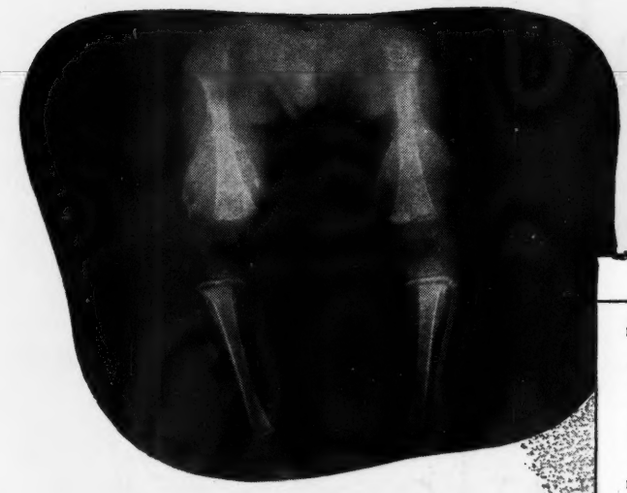
Casimir Funk Laboratories, Inc. (affiliate), 250 E. 43rd St., New York 17, N.Y.



AGE	NO. SUBJECTS EXAMINED	NO. WITH SCURVY	% WITH SCURVY	NO. WHITE SUBJECTS	NO. WITH SCURVY	NO. NEGRO SUBJECTS	NO. WITH SCURVY
0–15 da.	360	0	0	174	0	186	0
16–30 da.	90	1	—	41	1	49	0
1 mo.	99	0	0	48	0	51	0
2 mo.	90	2	2.2	34	2	56	0
3 mo.	69	3	4.3	31	3	38	0
4 mo.	79	2	2.5	26	1	53	1
5 mo.	73	12	16.5	25	3	48	9
6 mo.	53	13	24.5	19	5	34	8
7 mo.	54	10	18.5	22	7	32	3
8 mo.	40	5	12.5	18	2	22	3
9 mo.	38	10	26.3	12	4	26	6
10 mo.	41	5	12.2	16	0	25	5
11 mo.	40	3	7.5	12	0	28	3
12–23 mo.	177	3	—	68	1	109	2
Total.....	1303	69		546	29	757	40

PREVALENCE OF SCURVY

SCURVY

is more common than many think

Histological examination* of bone structure in 1300 infant post mortems revealed that scurvy occurred more than 10 times as frequently as is usually shown by clinical diagnosis. The most susceptible age is from the fifth through the eleventh month, with approximately 17% of infants exhibiting the histological signs. Over half of the children with scurvy had never received supplemental vitamin C. How easy to prevent, when Florida citrus is so rich in vitamin C content — so convenient, so economical, and so pleasant to take!

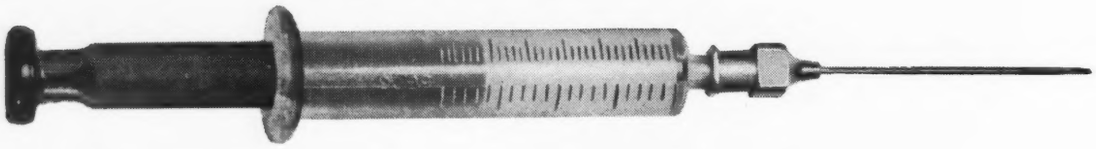
* *Bull. Johns Hopkins Hosp. 87:569, 1950.*

FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA

FLORIDA *Citrus*

ORANGES • GRAPEFRUIT • TANGERINES

therapeutic essentials for control



# of tuberculosis...

The range of new and older antibiotic and more effective chemotherapeutic agents available from Pfizer permits the clinician the widest choice in the selection of therapy most appropriate for the individual patient. Convenient dosage forms of Pfizer antituberculosis agents include:

new **COMBISTREP*** A combination of equal parts of streptomycin and dihydrostreptomycin: dry powder in 1 Gm. and 5 Gm. vials.

STREPTOHYDRAZID* A crystalline compound combining streptomycin (1 Gm.) with isoniazid (236 mg.) for single injection therapy: in single-dose vials containing 1.4 Gm. Streptohydrazid.

VIOCIN* *(sulfate)* For resistant cases of tuberculosis: in single-dose vials containing 1 Gm. viomycin.

STREPTOMYCIN *(sulfate)* Available as powder and solution for individual regimens: dry powder in 1 Gm. and 5 Gm. vials; solution in 1 Gm. and 5 Gm. vials and in single-dose (1 Gm.) Steraject® disposable cartridges.

DIHYDROSTREPTOMYCIN *(sulfate)* Available as powder and solution for individual regimens: dry powder in 1 Gm. and 5 Gm. vials; solution in 1 Gm. and 5 Gm. vials and in single-dose (1 Gm.) Steraject disposable cartridges.

COTINAZIN® Crystalline isoniazid for oral administration: in 50 mg. tablets in bottles of 100 and 1000.

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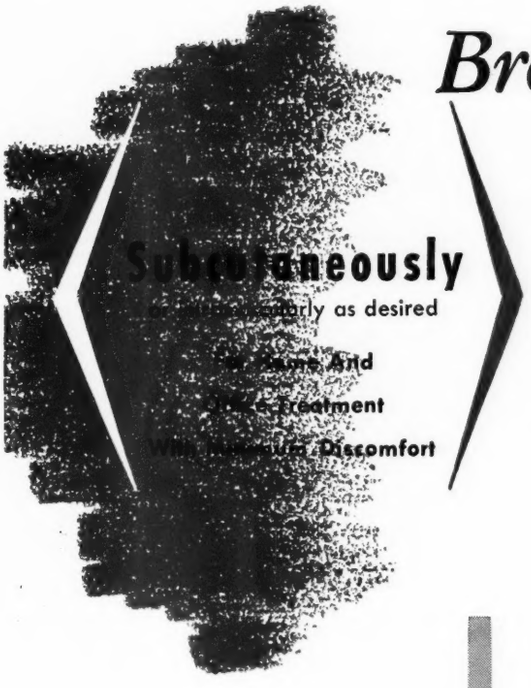
IN RESEARCH
AND
DEVELOPMENT
OF
ANTITUBERCULOSIS
AGENTS

Significant Simplification in the Routine Management of *Bronchial Asthma*



HP*ACTHAR *Gel*

(IN GELATIN)

*Highly Purified. ACTHAR® is The Armour Laboratories Brand of Adrenocorticotropic Hormone—ACTH (Corticotropin).

Self-administered As Easily As Insulin:
A Patient Treated With HP*ACTHAR *Gel*

A woman 36 years of age had to be hospitalized five times in 18 months for severe status asthmaticus which usually developed after each respiratory infection.

The problem of recurrent attacks was effectively controlled when the patient was taught self-administration of HP*ACTHAR *Gel*. She has given herself five courses of HP*ACTHAR *Gel* during the past year. Each course took from 3 to 5 days, and the results were so satisfactory that *no hospitalization was required.*

(Levin, S. J.: Ann. Allergy 11: 157-169, 1953; Case 6)

Advantages of HP*ACTHAR *Gel*

Fewer Injections:

One or two doses per week in many instances.

Rapid Response, Prolonged Effect:

Combines the two-fold advantage of sustained action over prolonged periods of time with the quick response of lyophilized ACTHAR.

Much Lower Cost:

Recent significant reduction in price, and reduced frequency of injections, have advanced economy of ACTH treatment.

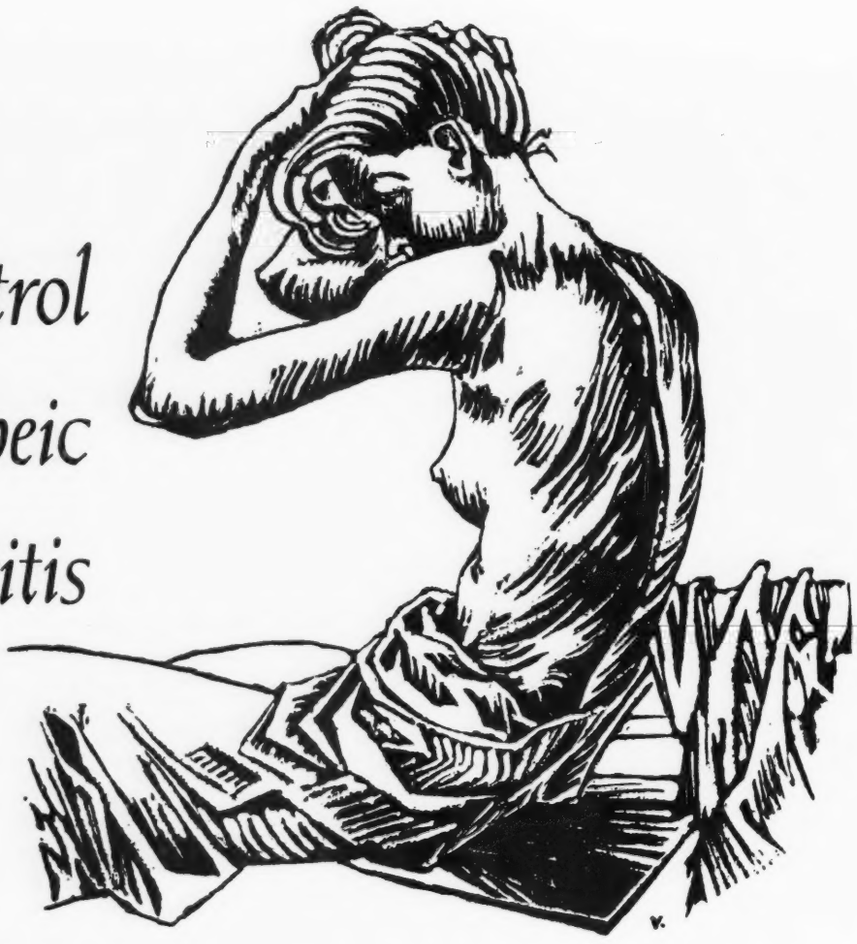
THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY · CHICAGO 11, ILLINOIS

world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH RESEARCH

Control seborrheic dermatitis



WITH

. . . a product you *know* is effective

. . . a product patients will use

No tedious application and removal procedures, no discomforting ointments, no stains on clothing or linens complicate SELSUN Sulfide Suspension's effective control of seborrheic dermatitis of the scalp. Its encouraging results further assure patient cooperation. SELSUN maintains control of scaling for one to four weeks, stops itching after two or three applications. Clinical investigators[1-3] reported complete control in 81 to 87 per cent of all cases of seborrheic dermatitis, and in 92 to 95 per cent of common dandruff cases. In 4-fluidounce bottles, SELSUN is ethically advertised and dispensed on prescription only.

Abbott

prescribe SELSUN®

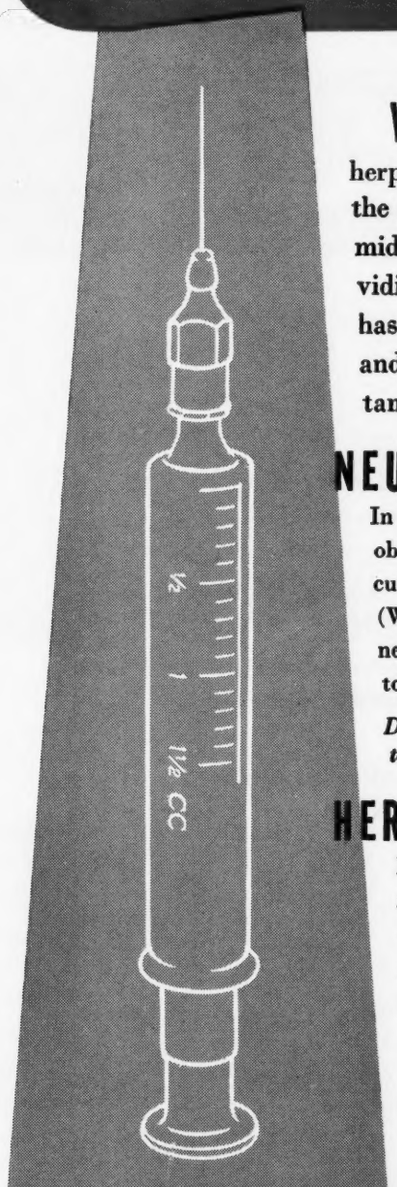
SULFIDE Suspension

(Selenium Sulfide, Abbott)

1. Slepyan, A. H. (1952), Arch. Dermat. & Syph., 65:228, February.
2. Slinger, W. N., and Hubbard, D. M. (1951), *ibid.*, 64:41, July.
3. Sauer, G. C. (1952), J. Missouri M.A., 49:911, November.

PROTAMIDE

FOR THE PATIENT SEEKING RELIEF FROM NERVE ROOT PAIN



WHEN the disturbing and painful symptoms of herpes zoster, or the stinging distress of neuritis brings the patient to you, quick relief is expected. Protamide helps solve this therapeutic problem by providing prompt and lasting relief in most cases. This has been established by published clinical studies, and on the valid test of patient-response to Protamide therapy in daily practice.

NEURITIS (Sciatic—Intercostal—Facial)

In a recent study* of 104 patients, complete relief was obtained in 80.7% with Protamide. 49 were discharged as cured after 5 days of therapy with no subsequent relapse. (Without Protamide, the usual course of the type of neuritis in this series has been found to be three weeks to over two months.)

Dosage: one 1.3 cc. ampul intramuscularly, daily for five to ten days.

HERPES ZOSTER

A study* of fifty patients with Protamide therapy resulted in excellent or satisfactory response in 78%. (No patient who made a satisfactory recovery suffered from postherpetic neuralgia.) Thirty-one cases of herpes zoster were treated with Protamide in another study.* Good to excellent results were obtained in 28.

Dosage: one 1.3 cc. ampul intramuscularly, daily for one to four or more days.

* *A folio of reprints of these studies will be sent on request.*

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS
WINDSOR · DETROIT 15, MICH. · LOS ANGELES

NEW... council-accepted oral anticoagulant

(not a coumarin derivative)

with a wide range of safety

HEDULIN®

(Brand of Phenindione, 2-phenyl-1,3-indandione)

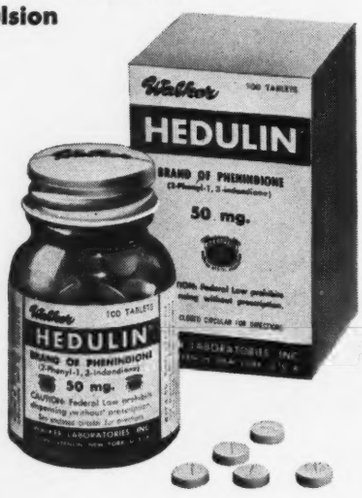
ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Permits dependable prothrombin control with little risk of dangerous fluctuations

- **HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance**
- **HEDULIN is rapidly excreted—therapeutic effect dissipated within 24-48 hours if withdrawal becomes necessary**
- **HEDULIN acts promptly, producing therapeutic prothrombin levels in 18-24 hours**
- **HEDULIN requires fewer prothrombin determinations—only one in 7 to 14 days, after maintenance dose is established**
- **HEDULIN's anticoagulant action is rapidly reversed by vitamin K_1 emulsion**

DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. daily, divided as above.

Available on prescription through all pharmacies, in original bottles of 100 and 1000 50-mg. scored tablets.



Complete literature to physicians on request

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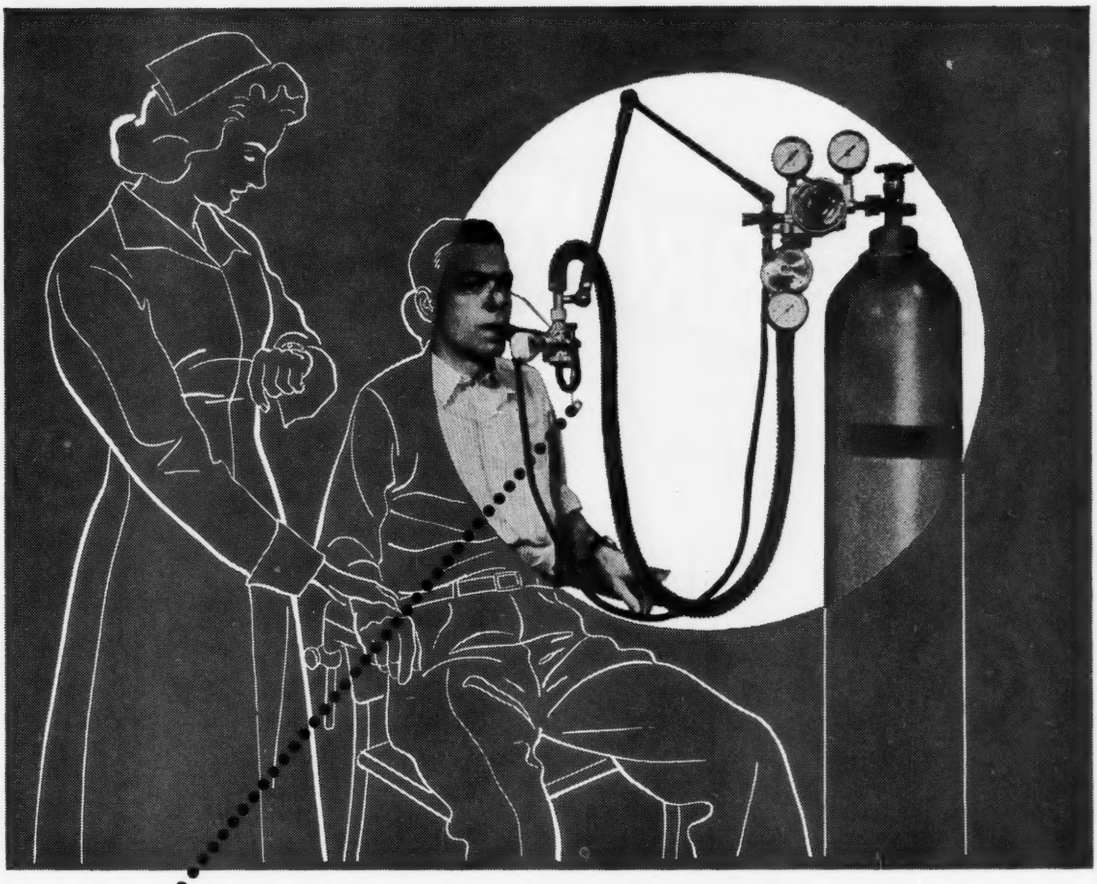

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Nicotinamide (2 X RDA†)	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
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*Minimum Daily Requirement

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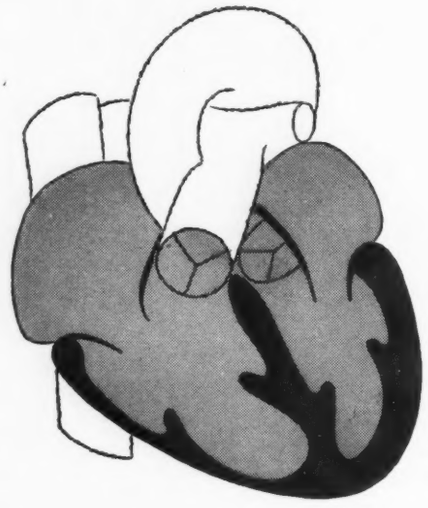
for dependable digitalization and maintenance when the oral route is unavailable



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is indicated for patients who are comatose, nauseated or uncooperative, or whose condition precludes the use of the oral route.

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provides all the unexcelled virtues of its parent oral preparation.

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*Strauss, V.; Simon, D. L.; Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent, Am. Heart J. 44:787, 1952.

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a specific use in

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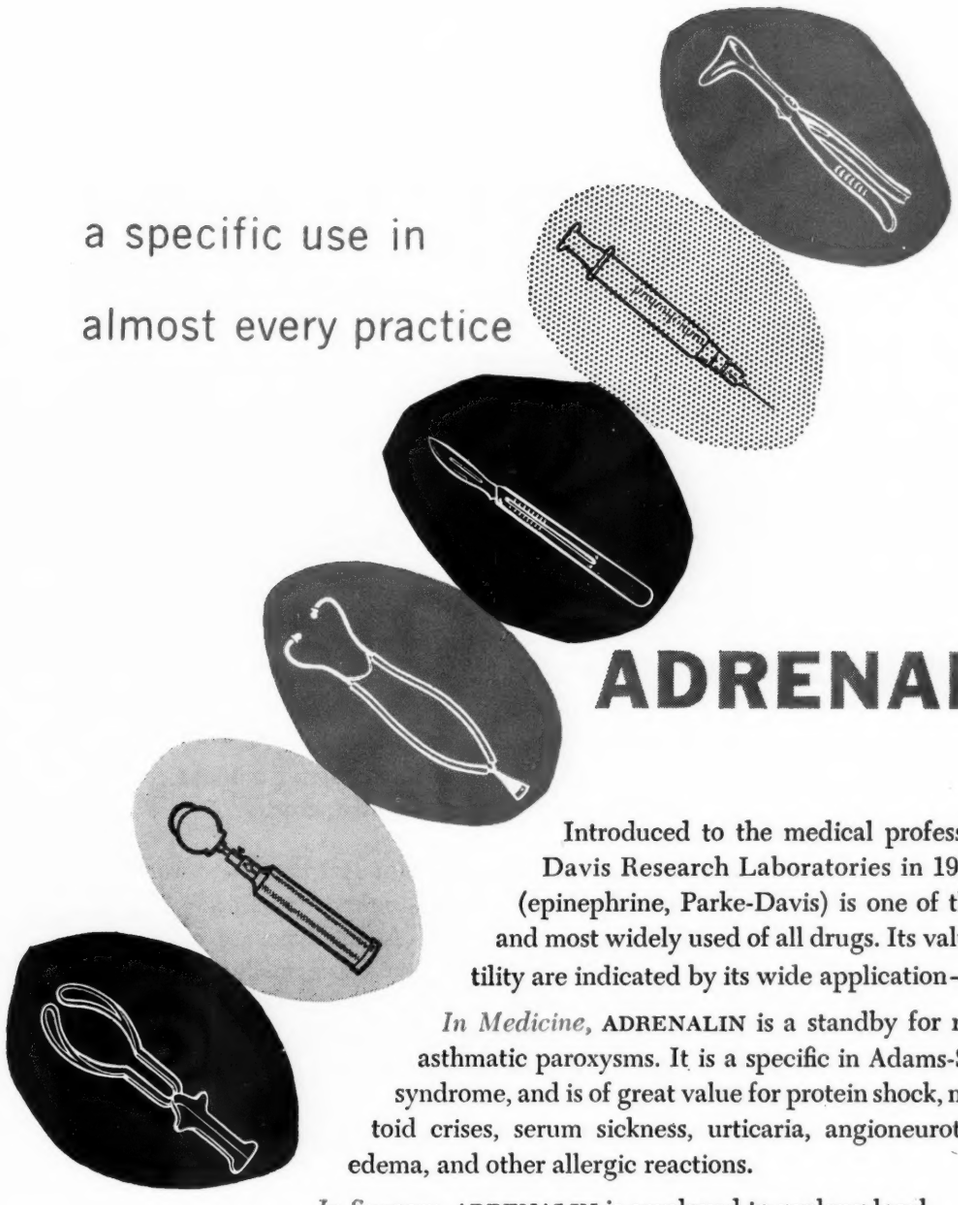

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ADRENALIN is available as ADRENALIN Chloride Solution 1:1000, ADRENALIN Chloride Solution 1:100, ADRENALIN In Oil 1:500, ADRENALIN Ointment 1:1000, ADRENALIN Suppositories 1:1000, ADRENALIN Hypodermic Tablets 3/200 grain, and in a variety of other forms to meet medical and surgical requirements.

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Root of the rheumatic fever problem

"The early and adequate treatment of upper respiratory tract infection of streptococcic origin almost eliminates the possibility of a rheumatic attack."[1]

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In a study of 1,204 beta hemolytic streptococcic infections, Breese reported that adequate penicillin blood levels, maintained for a week or longer, clear the throat of streptococci and prevent recurrent infections. Bicillin, wrote Breese, ". . . seemed to accomplish these results in the home most satisfactorily."[2]

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Worthy of attention is the fact that there were only 6 reactions in studies reporting 3,159 injections of Bicillin, an incidence of about 0.2%.[3,4] Because it produces penicillin blood levels lasting two weeks and longer, Bicillin therapy means fewer injections and consequently less trauma to the patient.

SUPPLIED:

1 cc. Tubex®, 600,000 units (approximately 600 mg.) per cc.

10 cc. multiple-dose vials, 300,000 units (approximately 300 mg.) per cc.

References: *1. Primer on the rheumatic diseases; prepared by a committee of the American Rheumatism Association. Special article: J.A.M.A.* **152**:*323 (May 23) 1953. 2. Breese, B.B.: J.A.M.A.* **152**:*10 (May 2) 1953. 3. Stollerman, G.H.: J.A.M.A.* **150**:*1571 (Dec. 20) 1952. 4. O'Brien, J.F., and Smith, C.A.: Am. J. Syph., Gonor. & Ven. Dis.* **36**:*519 (Nov.) 1952.*

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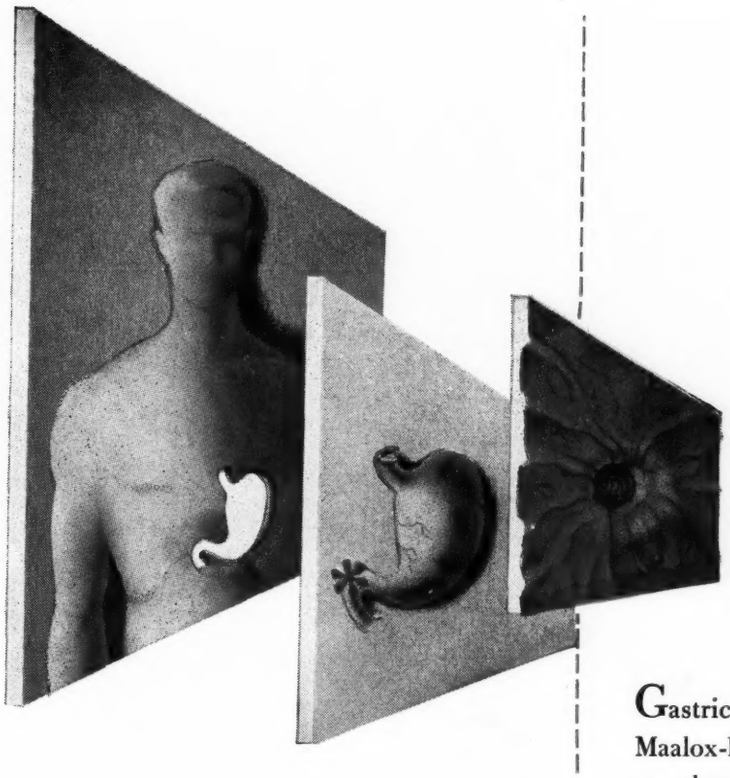

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September, 1953

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Anticholinergic with
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Prescribe Antrenyl in your next case of peptic ulcer and spasm of the gastrointestinal tract. Available as tablets, 5 mg., scored, bottles of 100; and syrup, 5 mg. per teaspoonful (4 cc.), bottles of 1 pint.

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sedation
antacids
nonirritating diet
anticholinergics

1. Rosser, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:150, 1952.